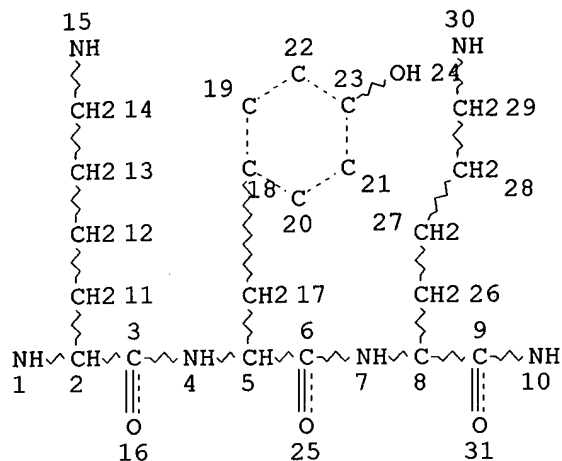


=> d que  
L10

STR



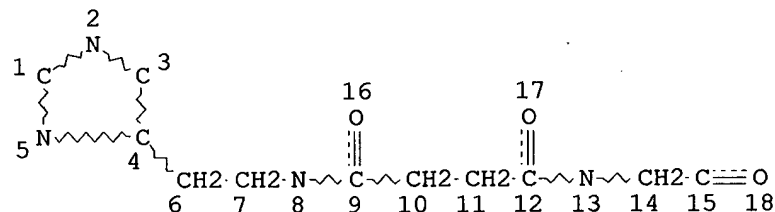
← core structure  
(Lys-Tyr-Lys)

NODE ATTRIBUTES:  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

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GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 31

STEREO ATTRIBUTES: NONE  
L12 631 SEA FILE=REGISTRY SSS FUL L10  
L15 STR



← HSG

NODE ATTRIBUTES:  
CONNECT IS E2 RC AT 8  
CONNECT IS E2 RC AT 13  
DEFAULT MLEVEL IS ATOM  
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:  
RING(S) ARE ISOLATED OR EMBEDDED  
NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE  
L17 36 SEA FILE=REGISTRY SSS FUL L15  
L21 9 SEA FILE=HCAPLUS ABB=ON PLU=ON L12 AND L17

=&gt; d ibib abs hitstr 121 1-9

L21 ANSWER 1 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:51893 HCAPLUS

DOCUMENT NUMBER: 136:123598

TITLE: Production and use of novel peptide-based agents for use with bi-specific antibodies

INVENTOR(S): Hansen, Hans J.; Griffiths, Gary L.; Leung, Shui-on; McBride, William J.; Qu, Zhengxing

PATENT ASSIGNEE(S): USA

SOURCE: U.S. Pat. Appl. Publ., 37 pp., Cont.-in-part of U. S. Ser. No. 337,756.

CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 14

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002006379	A1	20020117	US 2001-823746	20010403
WO 2002082041	A2	20021017	WO 2002-US10235	20020403

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:  
 US 1998-90142P P 19980622  
 US 1998-104156P P 19981014  
 US 1999-337756 A2 19990622  
 US 2001-823746 A 20010403

AB The present invention relates to a bi-specific antibody or antibody fragment having at least one arm that is reactive against a targeted tissue and at least one other arm that is reactive against a linker moiety. The linker moiety encompasses a hapten to which antibodies have been prep'd. The antigenic linker is conjugated to one or more therapeutic or diagnostic agents or enzymes. The invention provides constructs and methods for producing the bispecific antibodies or antibody fragments, as well as methods for using them.

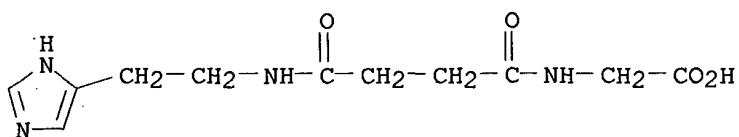
IT **192382-42-6D**, Histamine succinyl glycine, conjugates  
 RL: DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study);  
 USES (Uses)

(HSG; peptide-based diagnostic and therapeutic agents for use with bi-specific antibodies)

RN 192382-42-6 HCAPLUS

CN Glycine, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]- (9CI)  
 (CA INDEX NAME)

**BEST AVAILABLE COPY**



IT **389617-27-ODP**, triazacyclononanetriacetic acid thiol-contg. conjugates **389617-29-2DP**, triazacyclononanetriacetic acid thiol-contg. conjugates

RL: DGN (Diagnostic use); PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

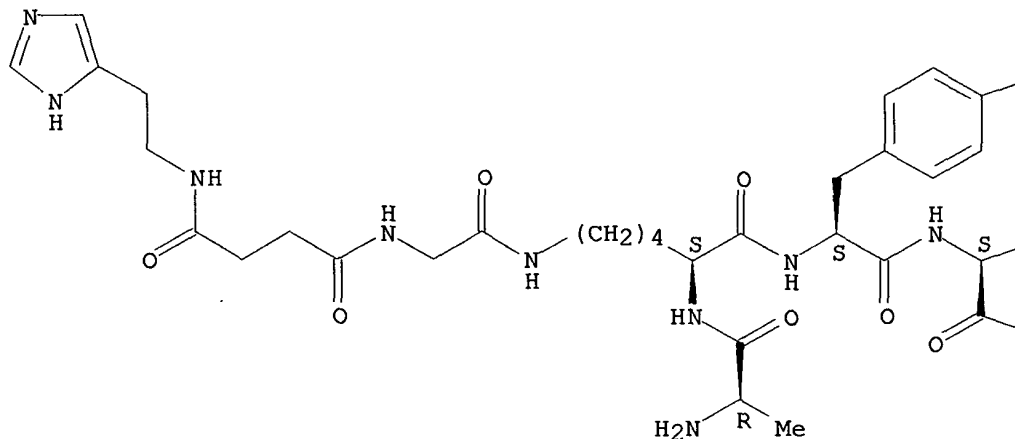
(peptide-based diagnostic and therapeutic agents for use with bi-specific antibodies)

RN 389617-27-0 HCAPLUS

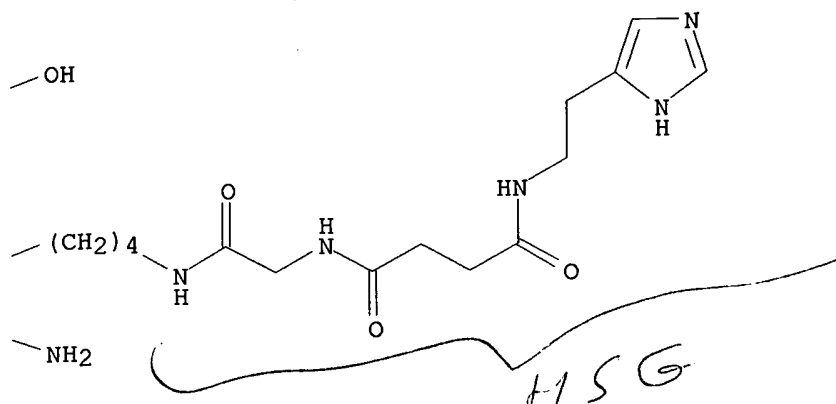
CN L-Lysinamide, D-alanyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-L-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

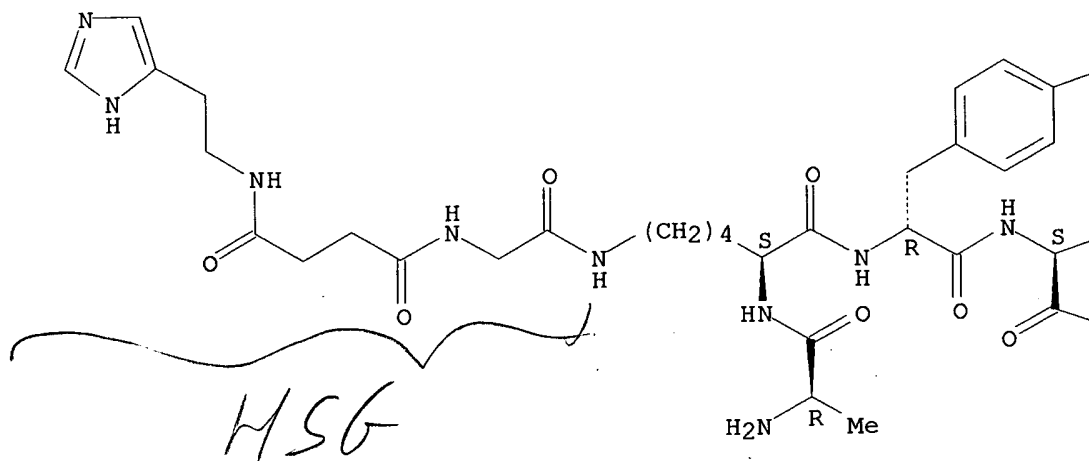


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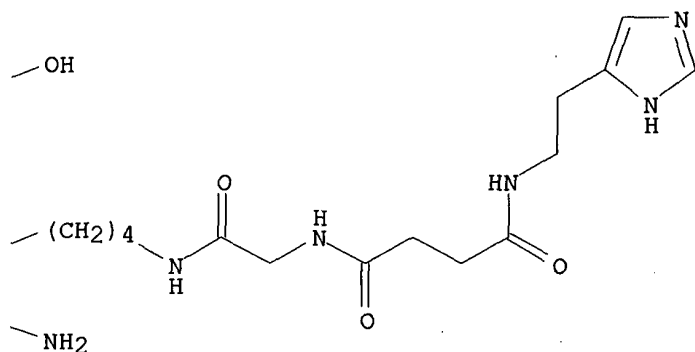
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



IT 391267-27-9P, IMP 241 391267-28-0P, IMP 237

391267-29-1P, IMP 243

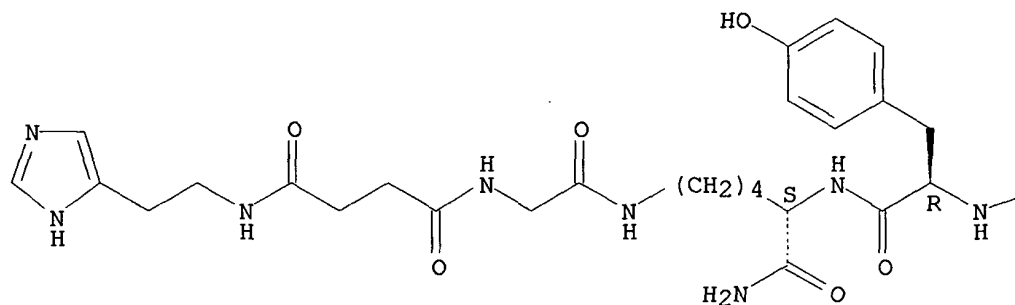
RL: DGN (Diagnostic use); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (peptide-based diagnostic and therapeutic agents for use with bi-specific antibodies)

RN 391267-27-9 HCAPLUS

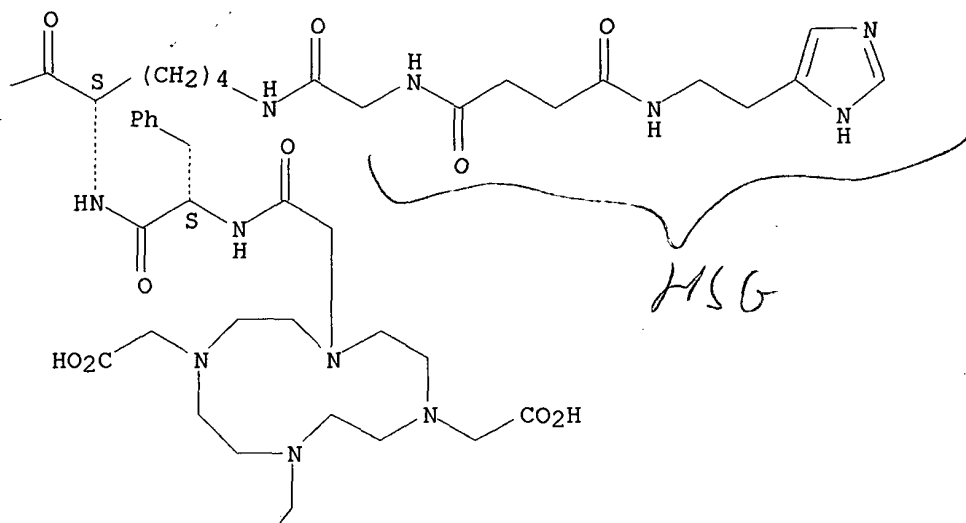
CN L-Lysinamide, N-[[4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododec-1-yl]acetyl]-L-phenylalanyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



PAGE 2-B

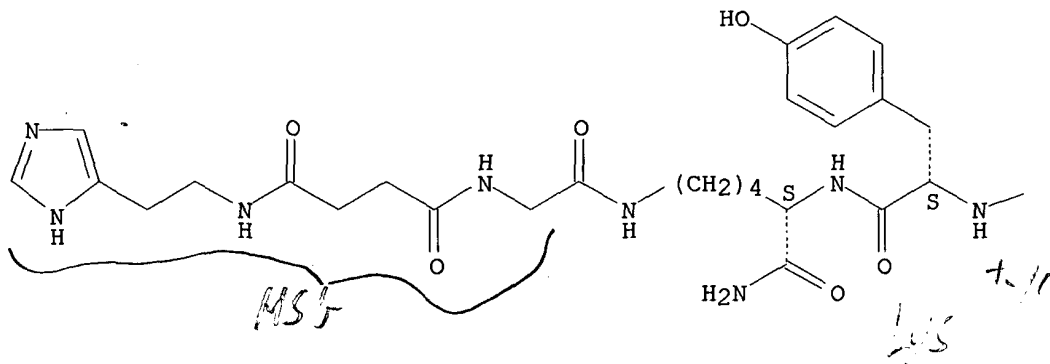
HO<sub>2</sub>C

RN 391267-28-0 HCAPLUS

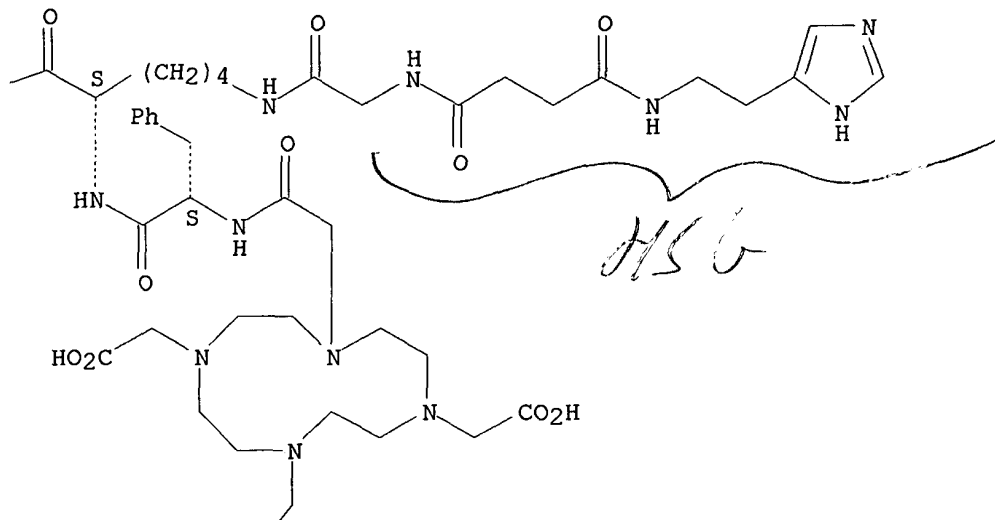
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



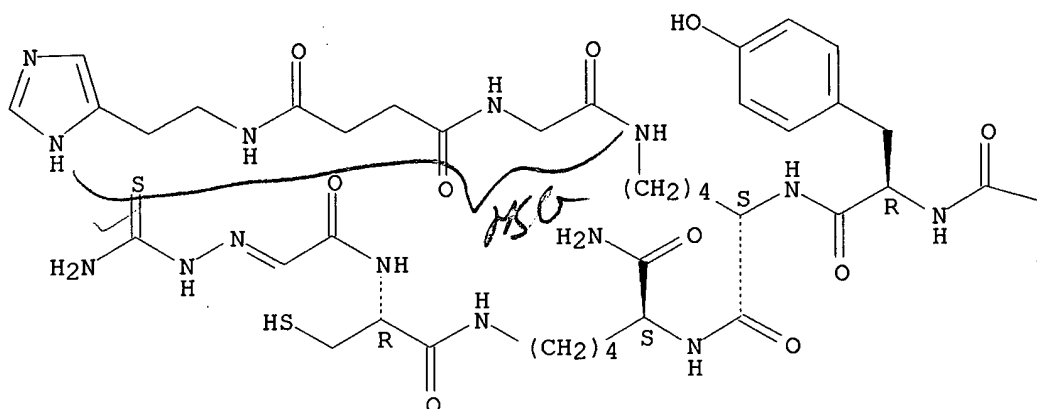
PAGE 2-B

HO<sub>2</sub>C

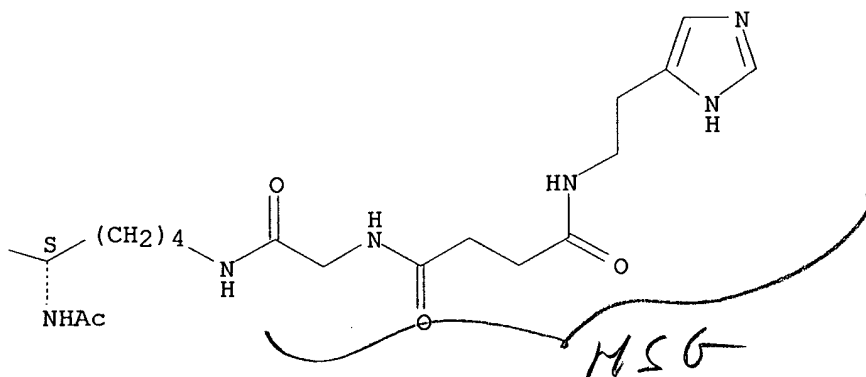
RN 391267-29-1 HCAPLUS  
 CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-N6-[N-[[ (aminothioxomethyl)hydrazono]acetyl]-L-cysteiny]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.  
 Double bond geometry unknown.

PAGE 1-A



PAGE 1-B



> L21 ANSWER 2 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2001:119457 HCAPLUS

DOCUMENT NUMBER: 135:177350

TITLE: Two-step targeting of xenografted colon carcinoma using a bispecific antibody and <sup>188</sup>Re-labeled bivalent hapten: Biodistribution and dosimetry studies

AUTHOR(S): Gestin, Jean F.; Loussouarn, Anthony; Bardies, Manuel; Gautherot, Emmanuel; Gruaz-Guyon, Anne; Sai-Maurel, Catherine; Barbet, Jacques; Curtet, Chantal; Chatal, Jean F.; Faivre-Chauvet, Alain

CORPORATE SOURCE: Institut de Biologie, Institut National de la Sante et de la Recherche Medicale, Nantes, 44093, Fr.

SOURCE: Journal of Nuclear Medicine (2001), 42(1), 146-153

CODEN: JNMEAQ; ISSN: 0161-5505

PUBLISHER: Society of Nuclear Medicine, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Radioimmunotherapy (RIT) is currently being considered for the treatment of solid tumors. Although results have been encouraging for pretargeted

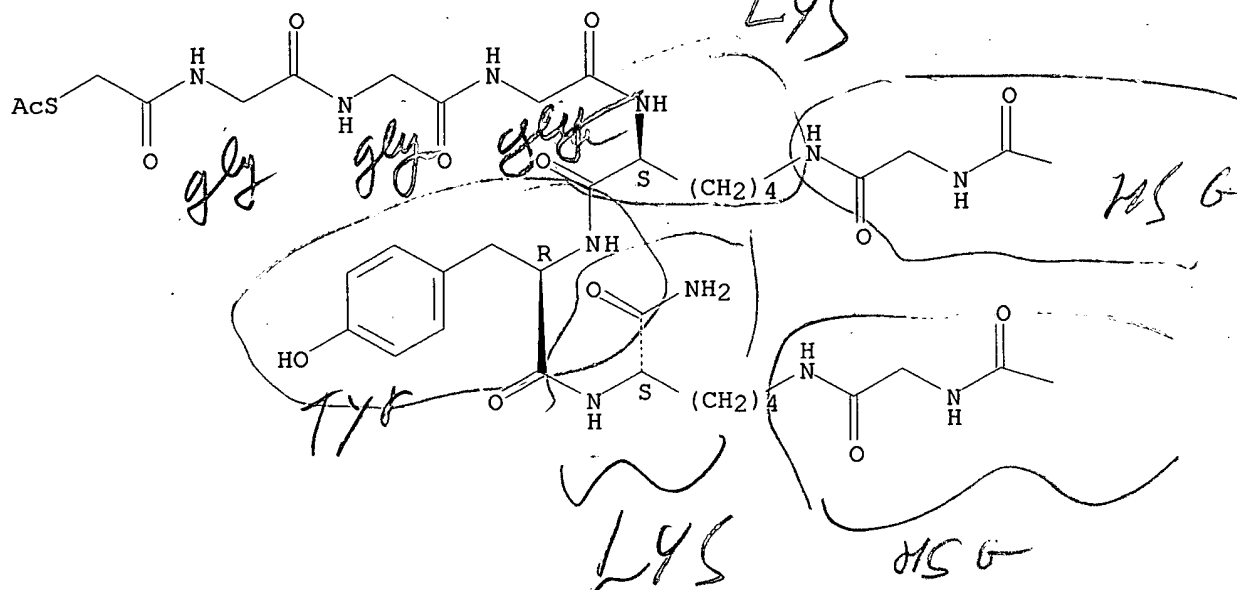


131I RIT with the affinity enhancement system (AES), the radionuclide used is not optimal because of its long half-life, strong .gamma. emission, poor specific activity, and low .beta. particle energy. 188Re, though unsuitable for direct antibody labeling, could be used with the AES two-step targeting technique. The purpose of this study was to compare the distribution and dosimetry of a bivalent hapten labeled with 188Re or 125I. For dosimetry calcns. and biodistribution data, 125I was substituted for 131I. After preliminary injection of a bispecific anticarcinoembryonic antigen (CEA) or antihapten antibody (Bs-mAb F6-679), AG 8.1 or AG 8.0 hapten radiolabeled with 188Re or 125I was injected into a nude mouse model grafted s.c. with a human colon carcinoma cell line (LS-174-T) expressing CEA. Not. A dosimetry study was performed for each animal from the concn. of radioactivity in tumor and different tissues. \*\* REG ADDED by mtd55 \*\*. Reg. Radiolabeling of AG 8.1 with 125I afforded a 40% yield with a specific activity of 11.1 MBq/nmol after purifn. Radiolabeling of AG 8.0 with 188Re afforded a 72% yield with a specific activity of 31.82 MBq/nmol. In all expts., the percentage of tumor uptake of 125I-AG 8.1 was always significantly greater than that of 188Re-AG 8.0. The corresponding tumor-to-tissue ratios reflected uptake values. The least favorable tumor-to-normal tissue ratios in the dosimetry study were 8.1 and 8.5 for 131I (tumor-to-blood ratio and tumor-to-kidney ratio, resp.) and 2.3 for 188Re (tumor-to-intestine ratio). This study indicates that 188Re can be used for radiolabeling of hapten in two-step radioimmunotherapy protocols with the AES technique. 188Re has a greater range than 131I, which should allow the treatment of solid tumors around 1 cm in diam. Although the method used for hapten radiolabeling did not provide optimal tumor uptake, the use of a bifunctional chelating agent assocd. with AG 8.1 should solve this problem.

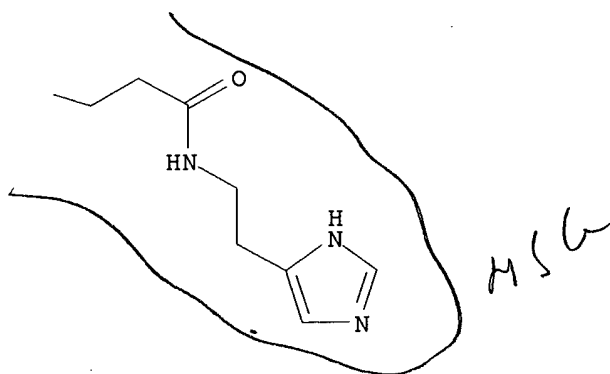
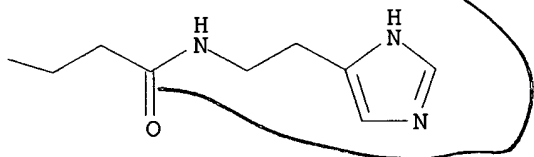
IT **159173-58-7DP**, 188Re-labeled **159173-61-2DP**, 125I-labeled  
 RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)  
 (targeting of colon carcinoma using bispecific antibody and 188Re-labeled bivalent hapten)  
 RN 159173-58-7 HCAPLUS  
 CN L-Lysinamide, N-[(acetylthio)acetyl]glycylglycylglycyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

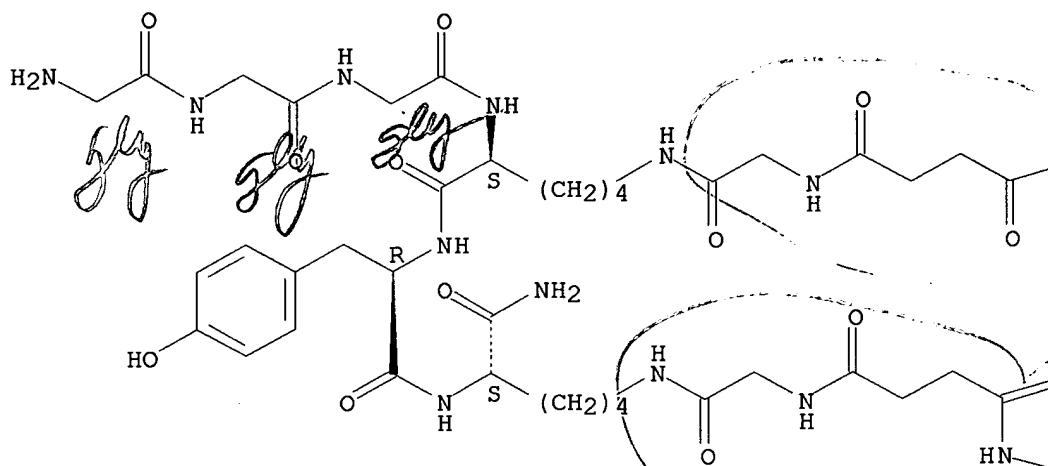


RN 159173-61-2 HCAPLUS

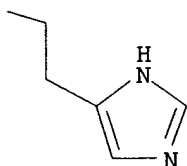
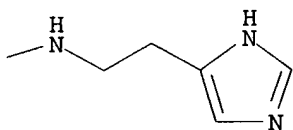
CN L-Lysinamide, glycylglycylglycyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT:

39

THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 3 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:

1999:479218 HCAPLUS

DOCUMENT NUMBER:

132:61055

TITLE:

Two-step targeting and dosimetry for small cell lung cancer xenograft with anti-NCAM/antihistamine

AUTHOR(S): bispecific antibody and radioiodinated bivalent hapten  
Hosono, Makoto; Hosono, Masako N.; Kraeber-Bodere,  
Francoise; Devys, Anne; Thedrez, Philippe;  
Faivre-Chauvet, Alain; Gautherot, Emmanuel; Barbet,  
Jacques; Chatal, Jean-Francois  
CORPORATE SOURCE: Saitama Medical Center, Saitama Medical School,  
Saitama, 350-8550, Japan  
SOURCE: Journal of Nuclear Medicine (1999), 40(7), 1216-1221  
CODEN: JNMEAQ; ISSN: 0161-5505  
PUBLISHER: Society of Nuclear Medicine, Inc.  
DOCUMENT TYPE: Journal  
LANGUAGE: English

AB The "affinity enhancement system," a two-step targeting technique using bispecific antibody and radiolabeled bivalent hapten, has been reported to be useful for carcinoembryonic antigen-expressing tumors. The purpose of this study was to evaluate the efficacy of this method for targeting human small cell lung cancer using an antineural cell adhesion mol. antibody. Methods: Antineural cell adhesion mol./antihistamine bispecific antibody NK1NBL1-679 was prepd. by coupling an equimol. quantity of a Fab' fragment of NK1NBL1 to a Fab fragment of antihistamine 679. Athymic mice inoculated with NCI-H69 small cell lung cancer cells expressing neural cell adhesion mol. were administered bispecific antibody and then 48 h later 125I-labeled bivalent histamine hapten. 125I-labeled intact NK1NBL1 was injected into other groups of mice. Biodistributions were examd. as a function of time. Results: In mice of the two-step targeting, tumor uptake was 2.5  $\pm$  0.2, 3.2  $\pm$  0.4, 6.4  $\pm$  2.0, 7.2  $\pm$  2.7, 6.1  $\pm$  2.1 and 2.2  $\pm$  0.4 %ID/g at 5, 30 min, 5, 24, 48 and 96 h, and tumor-to-blood, tumor-to-liver and tumor-to-kidney ratios were 1.4  $\pm$  1.1, 10.8  $\pm$  13.2 and 4.6  $\pm$  4.7, resp., at 5 h, whereas 125I-labeled NK1NBL1 showed a tumor uptake of 5.7  $\pm$  0.4 %ID/g and tumor-to-blood, tumor-to-liver and tumor-to-kidney ratios of 0.3  $\pm$  0.1, 1.1  $\pm$  0.2 and 0.9  $\pm$  0.1, resp., at 5 h. These results were confirmed by autoradiog. studies, which demonstrated clear tumor-to-normal tissue contrast. Dosimetry showed that the affinity enhancement system could enhance the therapeutic potential of the antineural cell adhesion mol. antibody NK1NBL1. Conclusion: This two-step targeting method seems promising for the diagnosis and therapy of small cell lung cancer.

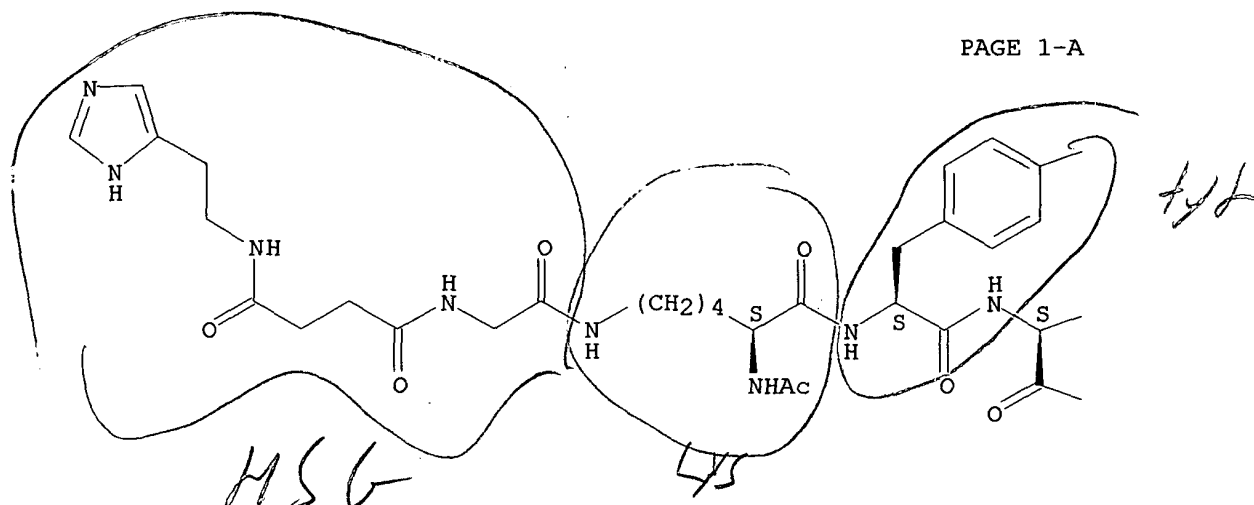
IT **136687-43-9D**, 125I-labeled  
RL: BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses) (two-step targeting and dosimetry for small cell lung cancer xenograft with anti-NCAM/antihistamine bispecific antibody and radioiodinated bivalent hapten)

RN 136687-43-9 HCAPLUS

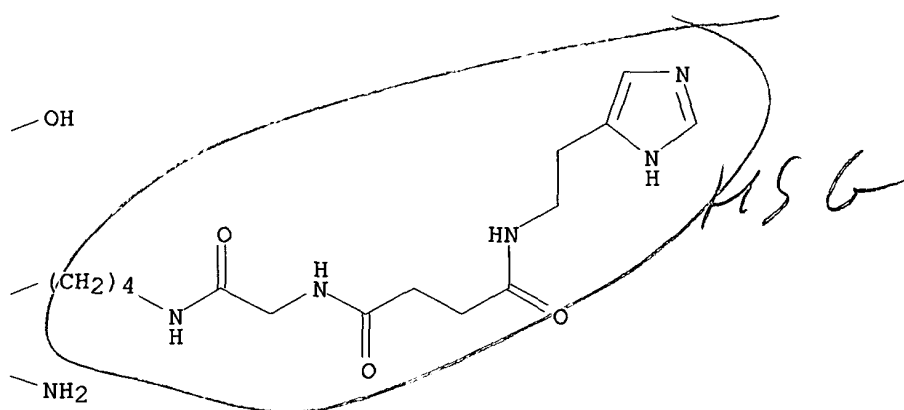
CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-L-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L21 ANSWER 4 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1998:81927 HCAPLUS

DOCUMENT NUMBER: 128:215043

TITLE: Pretargeted radioimmunotherapy using <sup>131</sup>I-labeled bivalent hapten-bearing peptides

AUTHOR(S): de Boisferon, Marc; Hillairet, Manetti, Corrine; Raguin, Olivier; Gautherot, Emmanuel; Rostene, William; Barbet, Jacques; Gruaz-Guyon, Anne  
 CORPORATE SOURCE: Hopital Fac. Med. Saint Antoine, Paris, F-75012, Fr.  
 SOURCE: Letters in Peptide Science (1997), 4(4/5/6), 331-339  
 CODEN: LPSCEM; ISSN: 0929-5666

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The advantages of bivalent hapten-bearing peptides for the detection of tumors pretargeted with bispecific antibodies have been demonstrated. This technol. is now considered for radioimmunotherapy and bivalent haptens designed to target <sup>131</sup>I are needed. We thus synthesized a series of tyrosine-contg. peptides bearing the histamine-hemisuccinate hapten.

These mols. were tested for their ability to bind simultaneously two anti-hapten antibody mols. One of these bivalent haptens, AG3.0, with a lysyl-D-tyrosyl-lysine-connecting chain, was found to have optimal binding characteristics and was thus selected for further investigations. AG3.0 was shown to efficiently deliver radioactive iodine to human colorectal tumors grafted in nude mice using an anti-carcinoembryonic antigen .times. anti-histamine-hemisuccinate bispecific antibody. AG3.0 was also targeted to human B lymphoma cells pretargeted with a bispecific antibody specific for membrane IgM. In this system, bivalent ligands such as F(ab')<sub>2</sub> or IgG are rapidly internalized and covalently linked radioactive iodine is released from target cells as a result of intracellular catabolism. With the pretargeted iodine-labeled bivalent hapten, a fivefold increase in the intracellular activity retention time as compared to 125I-labeled F(ab')<sub>2</sub> and IgG was obsd. The radiolabeled hapten did not undergo any degrdn. after internalization. These results have been confirmed in vivo with an anti-BCL1 IgM idiotype bispecific antibody and 131I-labeled AG3.0. These reagents injected as a single 300 .mu.Ci dose, 7 days after inoculation of 104 BCL1 lymphoma cells in BALB/c mice, cured 14/16 of the animals and the treatment was well tolerated. Comparatively, the same dose of labeled IgG cured 13/16 of the mice but three mice died of haematol. toxicity. The same dose of labeled F(ab')<sub>2</sub> or Fab' was completely inefficient. 131I-labeled bivalent haptens are now used in phase I radioimmunotherapy clin. trials.

IT 173039-12-8D, 131I-labeled

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

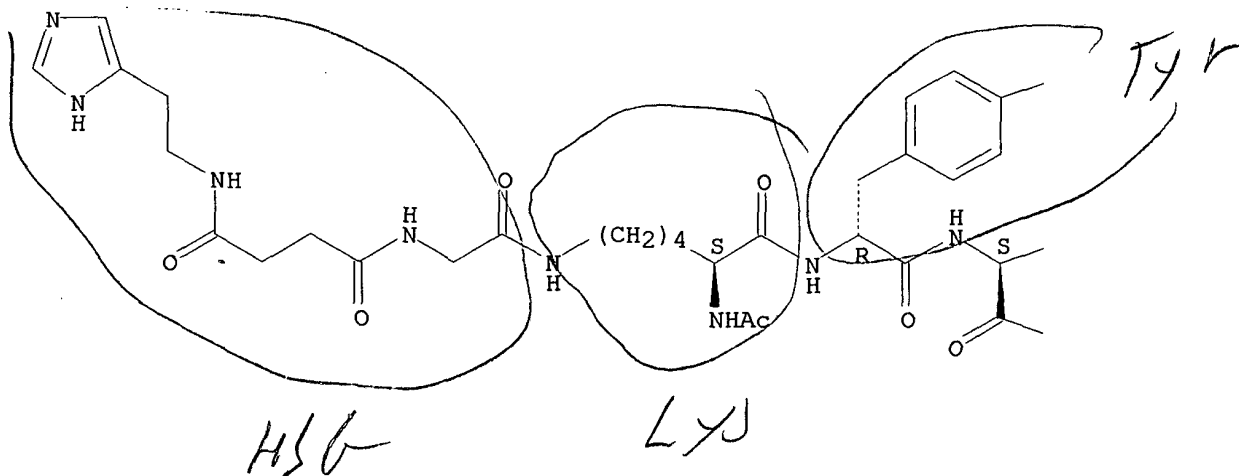
(pretargeted radioimmunotherapy using 131I-labeled bivalent hapten-bearing peptides)

RN 173039-12-8 HCAPLUS

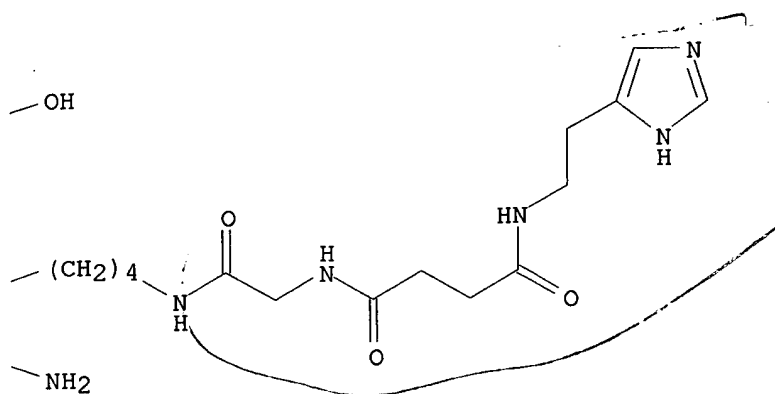
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Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



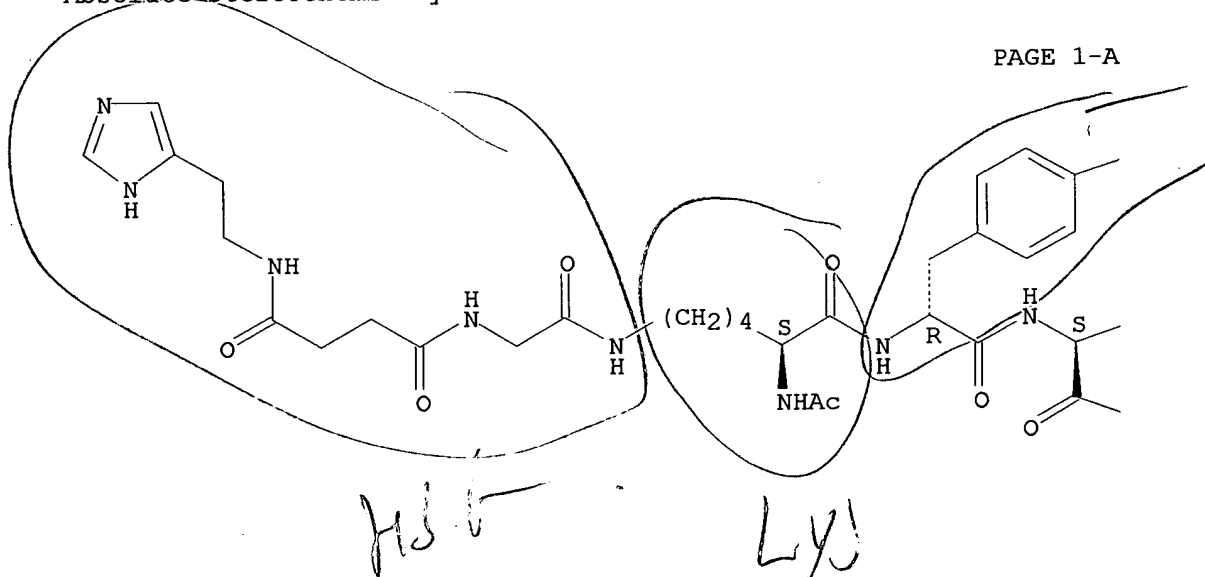
IT 173039-12-8 192370-39-1 192370-40-4  
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RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL  
 (Biological study); PROC (Process)  
 (pretargeted radioimmunotherapy using <sup>131</sup>I-labeled bivalent  
 hapten-bearing peptides)

RN 173039-12-8 HCAPLUS

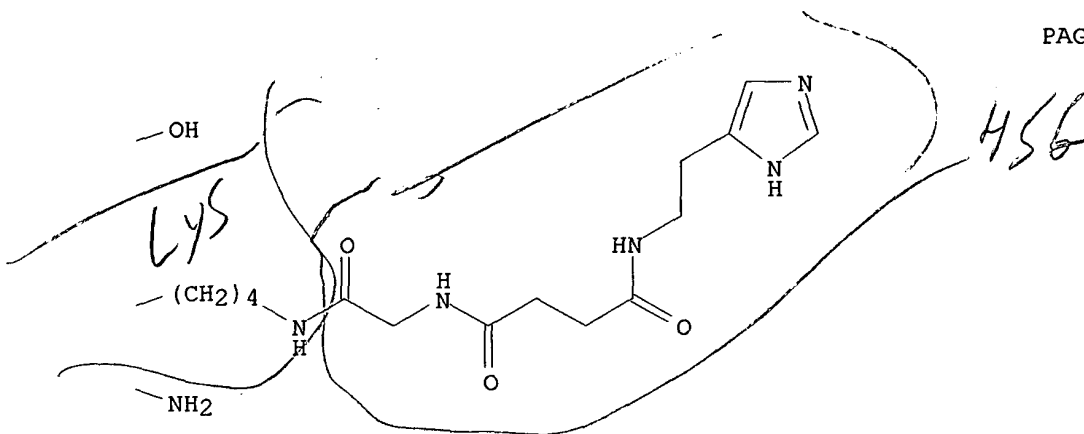
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Absolute stereochemistry.



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PAGE 1-B

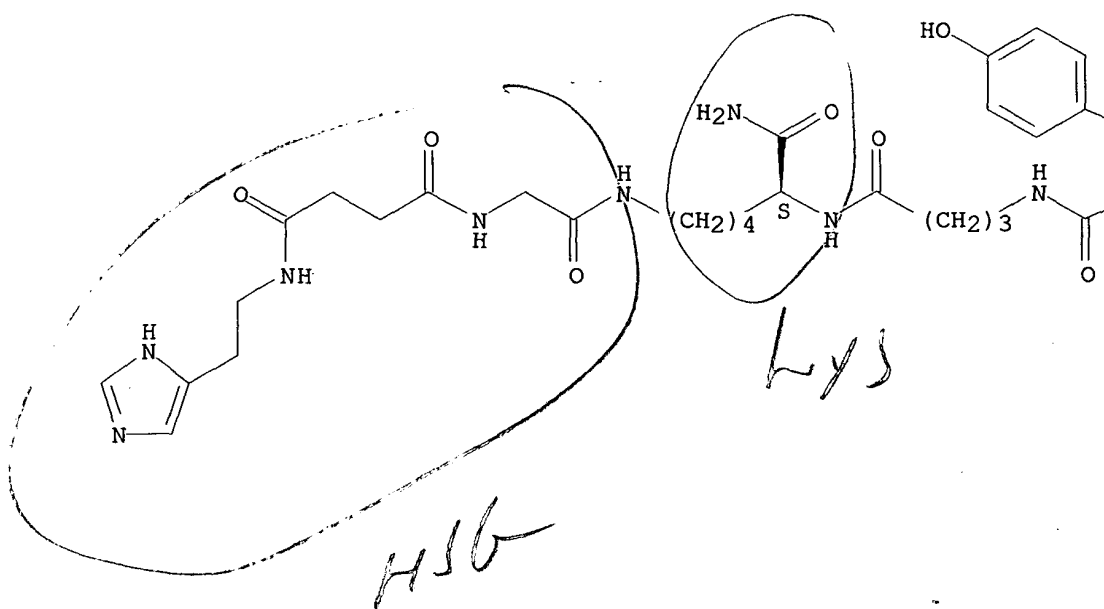


RN 192370-39-1 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-4-aminobutanoyl-D-tyrosyl-4-aminobutanoyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

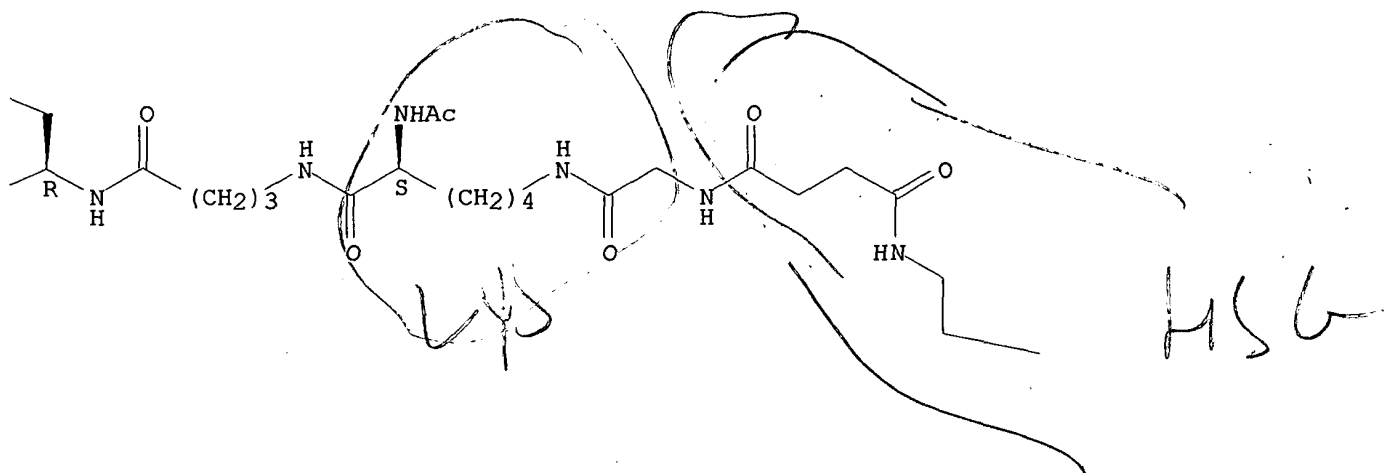
Absolute stereochemistry.

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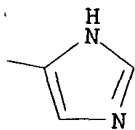




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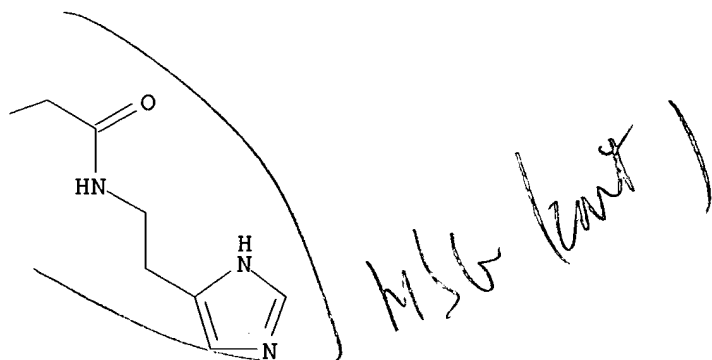
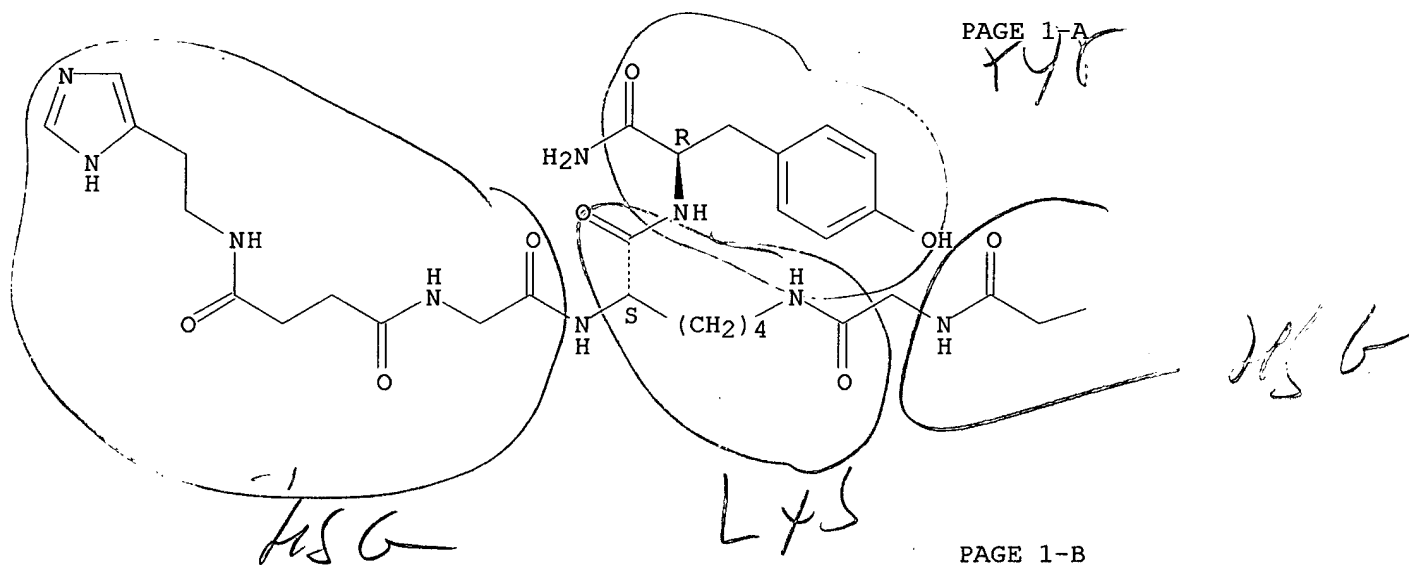
PAGE 1-C



RN 192370-40-4 HCAPLUS

CN D-Tyrosinamide, N2,N6-bis[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl- (9CI) (CA INDEX NAME)

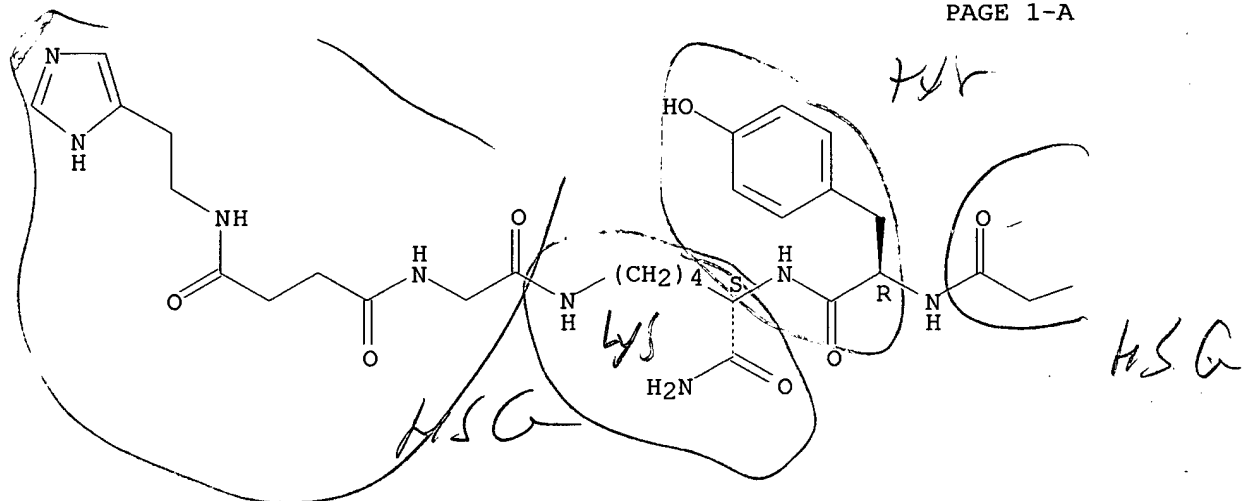
Absolute stereochemistry.



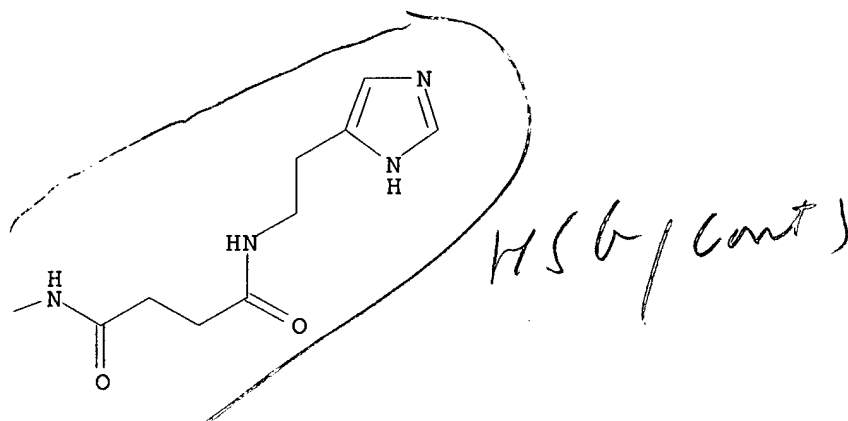
RN 192370-41-5 HCAPLUS  
 CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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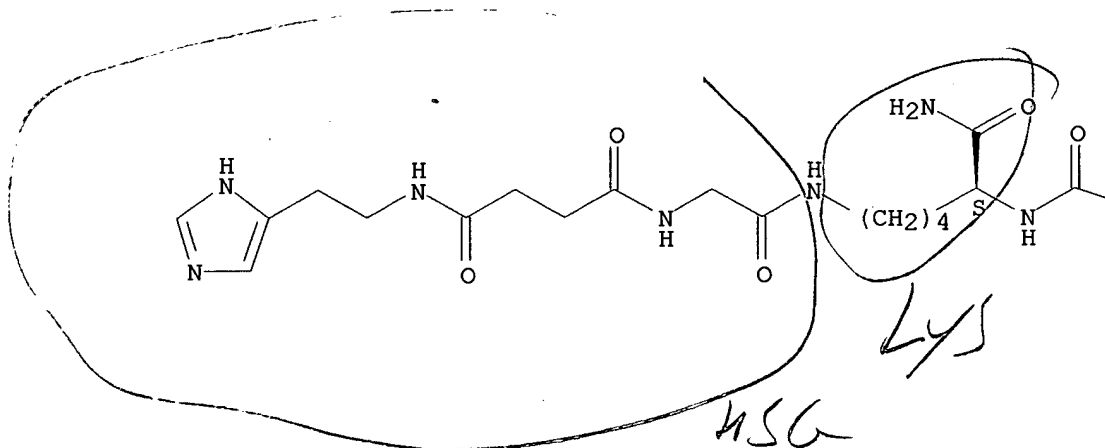


RN 192370-42-6 HCAPLUS

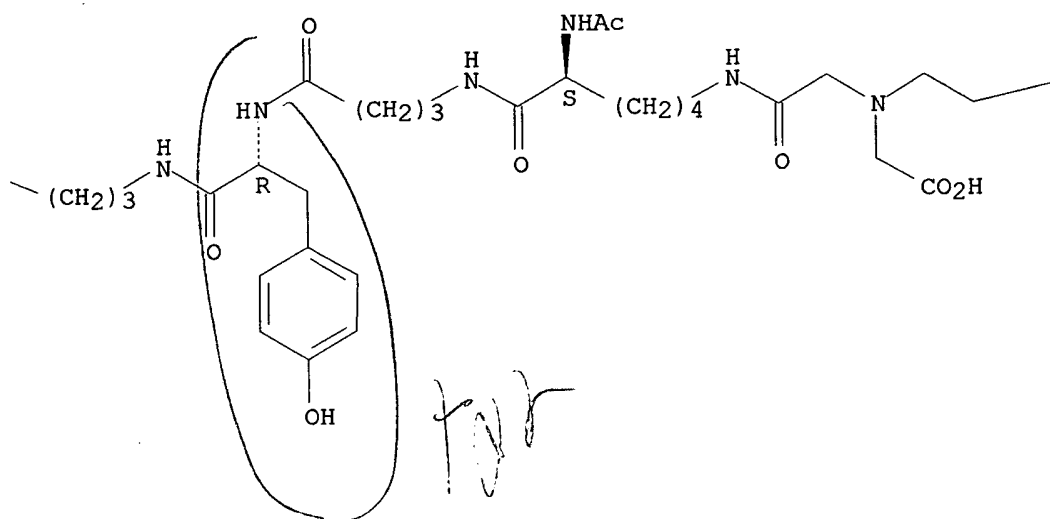
CN L-Lysinamide, N2-acetyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-4-aminobutanoyl-D-tyrosyl-4-aminobutanoyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

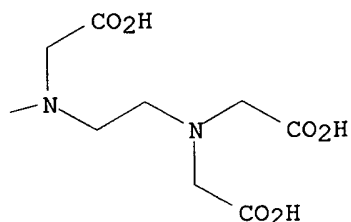
PAGE 1-A



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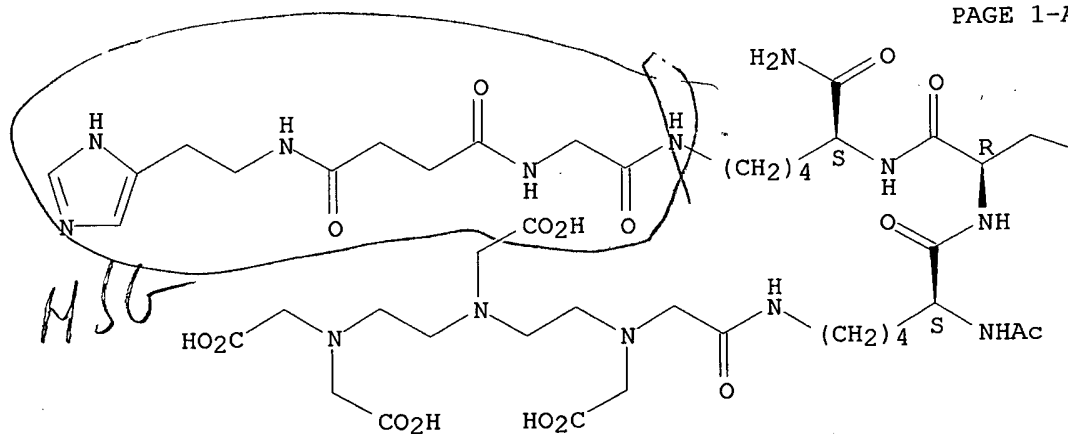


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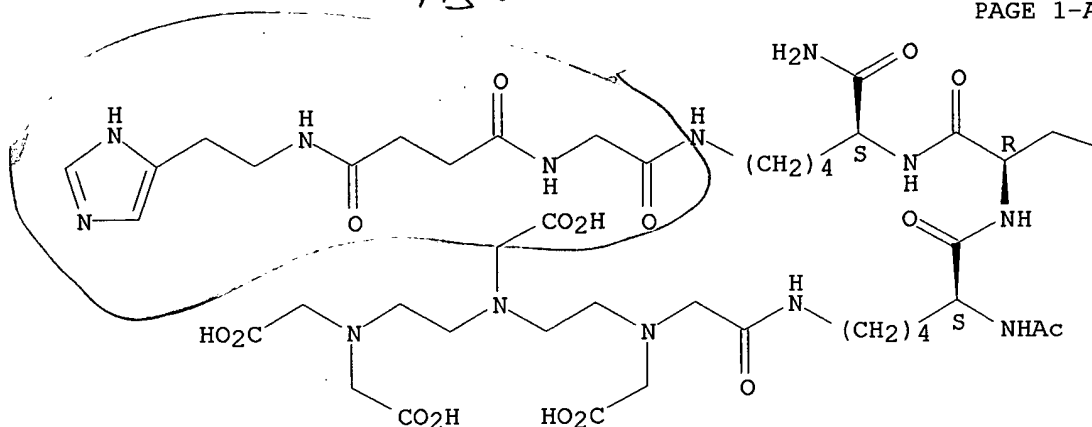
CN L-Lysinamide, N2-acetyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

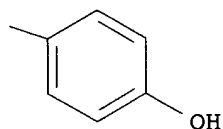
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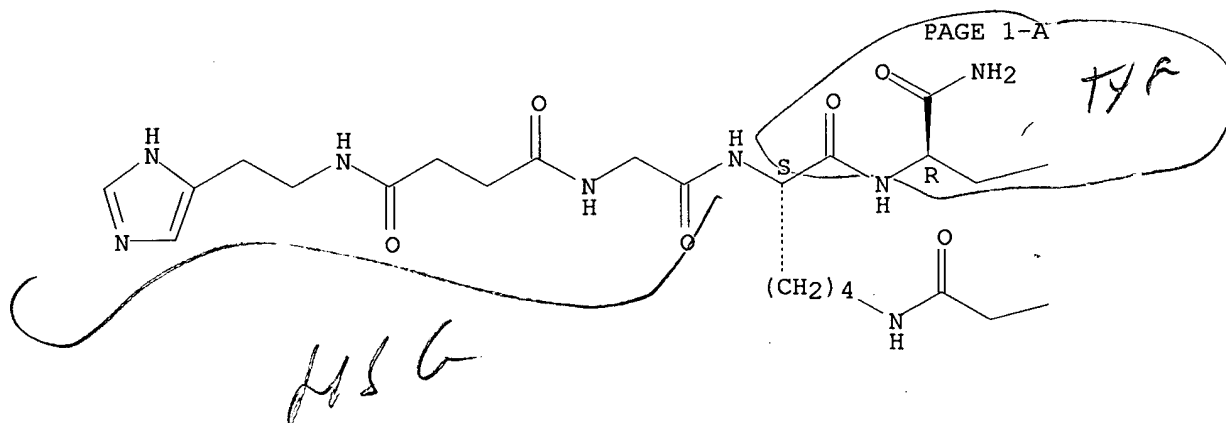


RN 192370-44-8 HCAPLUS

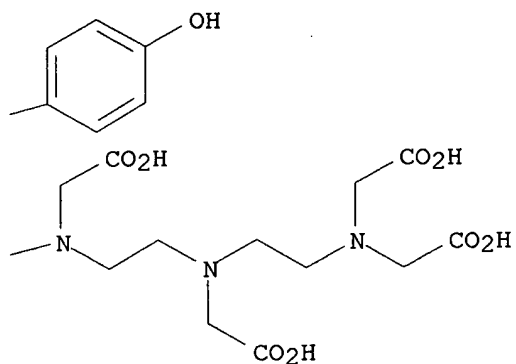
CN D-Tyrosinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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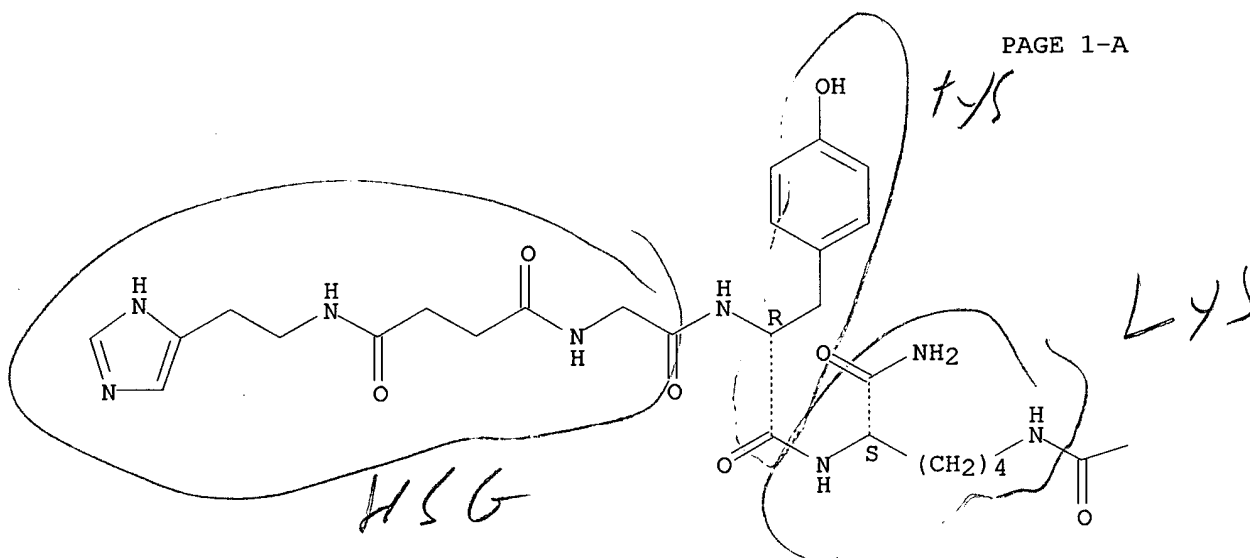


RN 192370-45-9 HCAPLUS

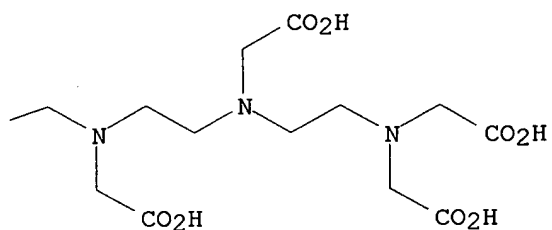
CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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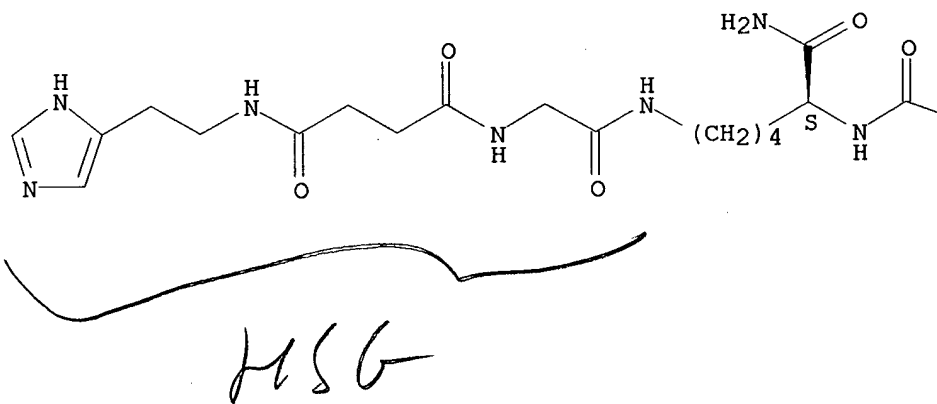


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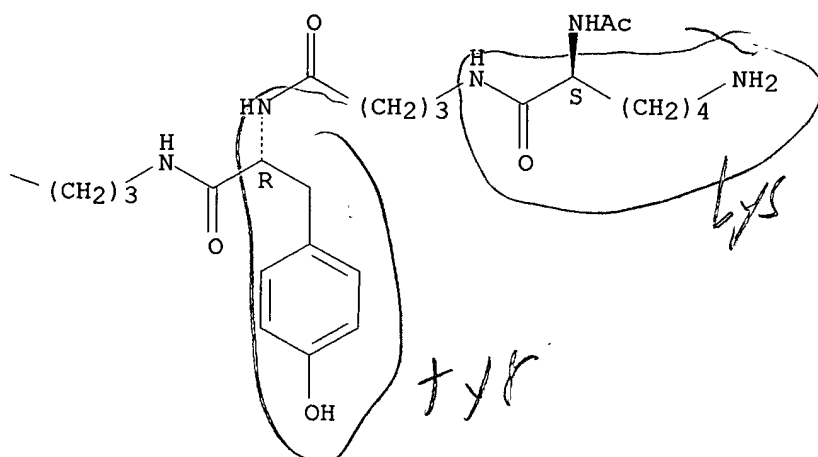
CN L-Lysinamide, N2-acetyl-L-lysyl-4-aminobutanoyl-D-tyrosyl-4-aminobutanoyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

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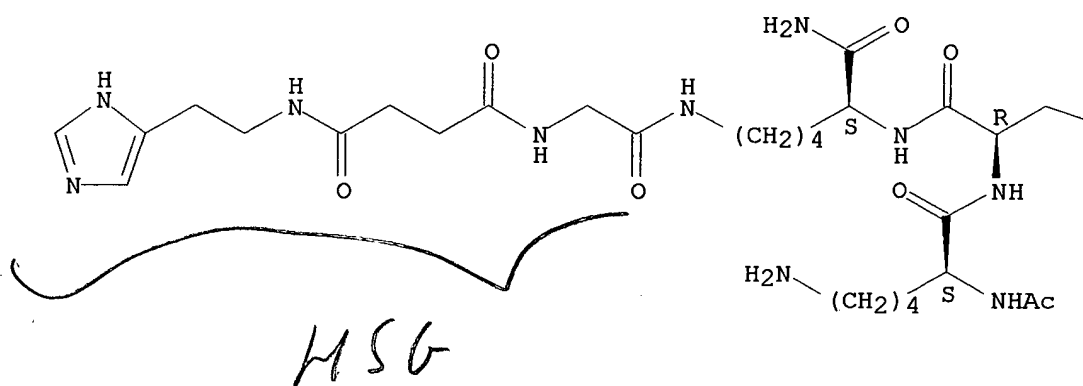


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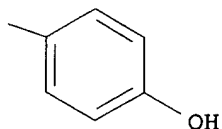
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Absolute stereochemistry.

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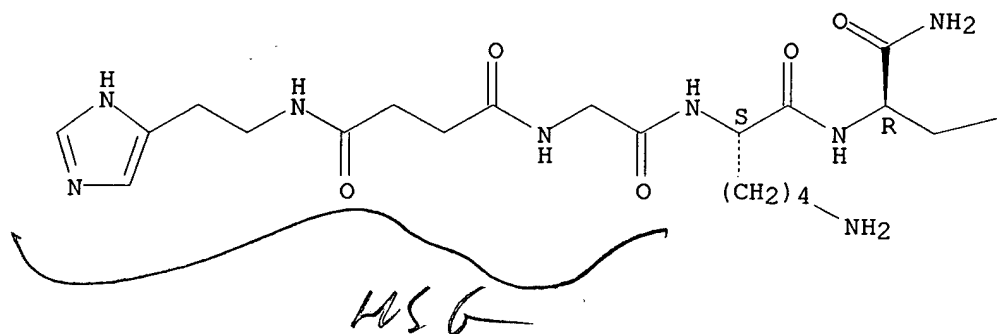
RN 192370-48-2 HCAPLUS

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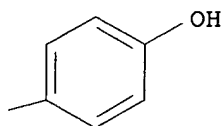
Absolute stereochemistry.



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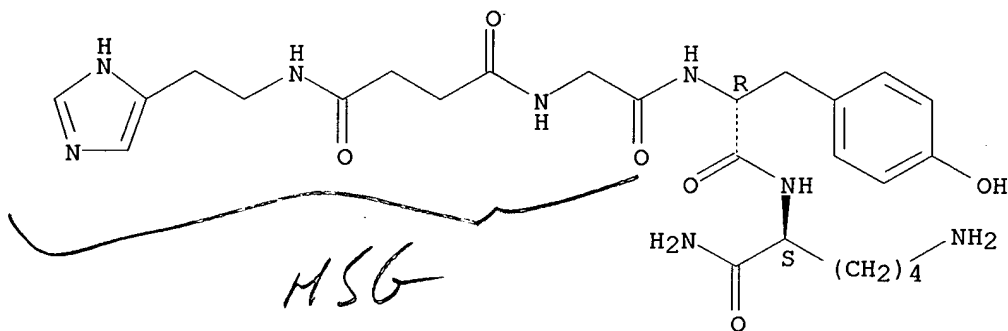
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RN 192370-49-3 HCAPLUS

CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L21 ANSWER 5 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1997:433597 HCAPLUS

DOCUMENT NUMBER: 127:106066

TITLE: Bivalent Hapten-Bearing Peptides Designed for

Iodine-131 Pretargeted Radioimmunotherapy

AUTHOR(S): Janevik-Ivanovska, E.; Gautherot, E.; de Boisferon, M.

Hillairet; Cohen, M.; Milhaud, G.; Tartar, A.;

Rostene, W.; Barbet, J.; Gruaz-Guyon, A.

CORPORATE SOURCE: INSERM U.339 and Service de Biophysique, Faculte de

Medecine Saint Antoine, Paris, 75012, Fr.

SOURCE: Bioconjugate Chemistry (1997), 8(4), 526-533

CODEN: BCCHES; ISSN: 1043-1802

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

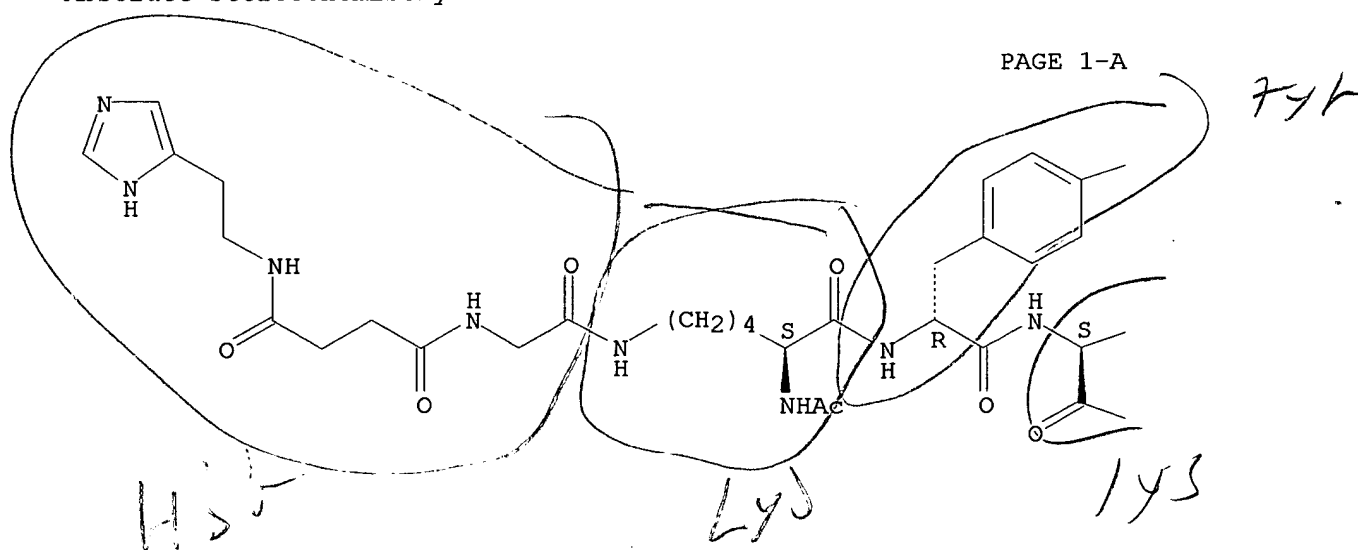
AB Pretargeting with bispecific antibodies has been used successfully for tumor detection and is now considered for radioimmunotherapy. The advantages of bivalent haptens have been demonstrated in this context. A series of bivalent mols. allowing efficient labeling with radioactive iodine has been designed for use with this new technol. They were based on the histamine-hemisuccinate hapten and prepd. by solid phase peptide synthesis. Simultaneous binding of two antibody mols. to one bivalent hapten was possible with low steric hindrance when the two hapten groups were attached to the lateral chains of lysine residues sepd. by a single amino acid. Bispecific antibodies to the hapten and to carcinoembryonic antigen were shown to mediate specific binding of the haptens to tumor cells in vitro. These expts. demonstrated that the bivalent hapten AG3.0, with a lysyl-D-tyrosyl-lysine connecting chain, possessed the best binding properties. This peptide was used to target iodine-125 to human colon cancer xenografts in nude mice. High tumor uptake and tumor to normal tissue ratios were obsd. This peptide thus appears as a good candidate for further development. Asym. bivalent haptens, with one histamine-hemisuccinate and one diethylenetriaminepentaacetic acid group, have also been prepd. and shown to be capable of binding simultaneously two specific antibody mols. These peptides should be useful to target radioiodine to cells characterized by the expression of two different antigenic markers.

IT 173039-12-8DP, labeled with iodine-131 192370-39-1DP, labeled with iodine-131 192370-40-4DP, labeled with iodine-131 192370-41-5DP, labeled with iodine-131 192370-42-6DP, labeled with iodine-131 192370-43-7DP, labeled with iodine-131 192370-44-8DP, labeled with iodine-131 192370-45-9DP, labeled with iodine-131 192370-46-0DP, labeled with iodine-131 192370-47-1DP, labeled with iodine-131 192370-48-2DP, labeled with iodine-131 192370-49-3DP, labeled with iodine-131  
 RL: PNU (Preparation, unclassified); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)  
 (bivalent hapten-bearing peptides designed for iodine-131 pretargeted radioimmunotherapy of colon carcinoma)

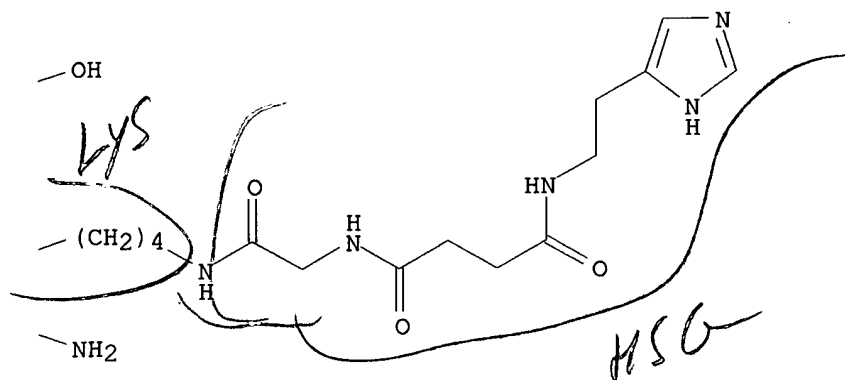
RN 173039-12-8 HCAPLUS

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Absolute stereochemistry.



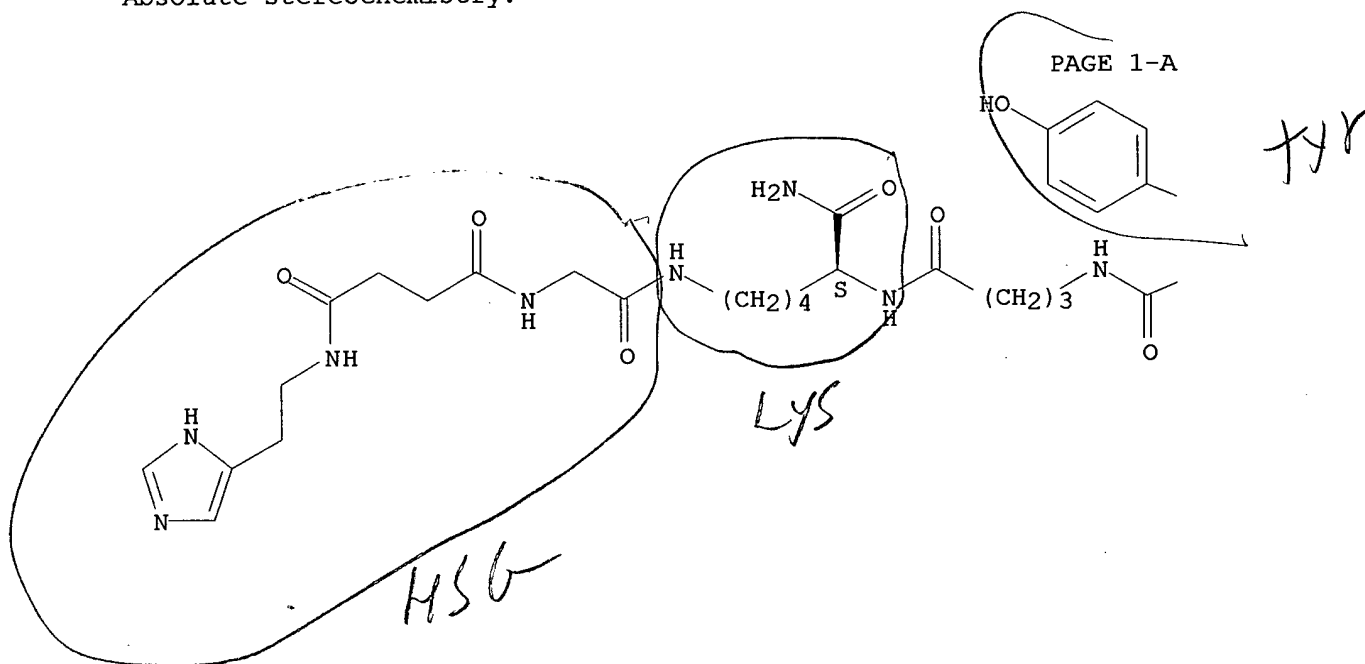
PAGE 1-B



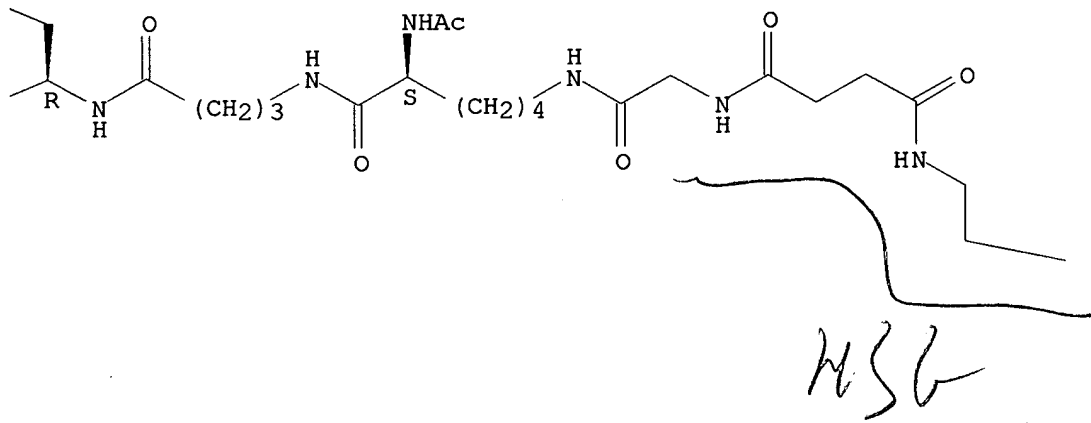
RN 192370-39-1 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-4-aminobutanoyl-D-tyrosyl-4-aminobutanoyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

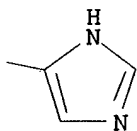
Absolute stereochemistry.



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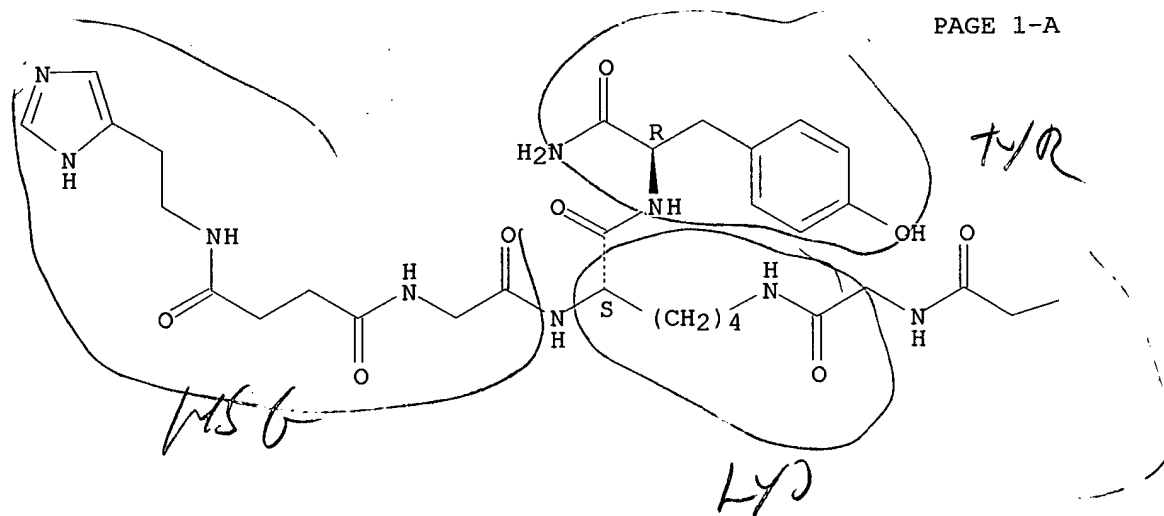


RN 192370-40-4 HCAPLUS

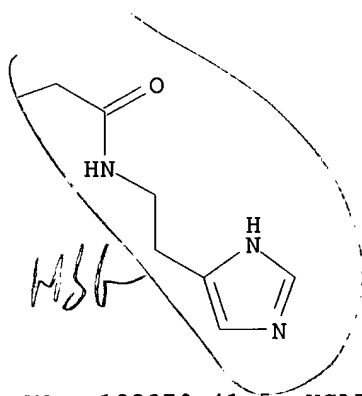
CN D-Tyrosinamide, N2,N6-bis[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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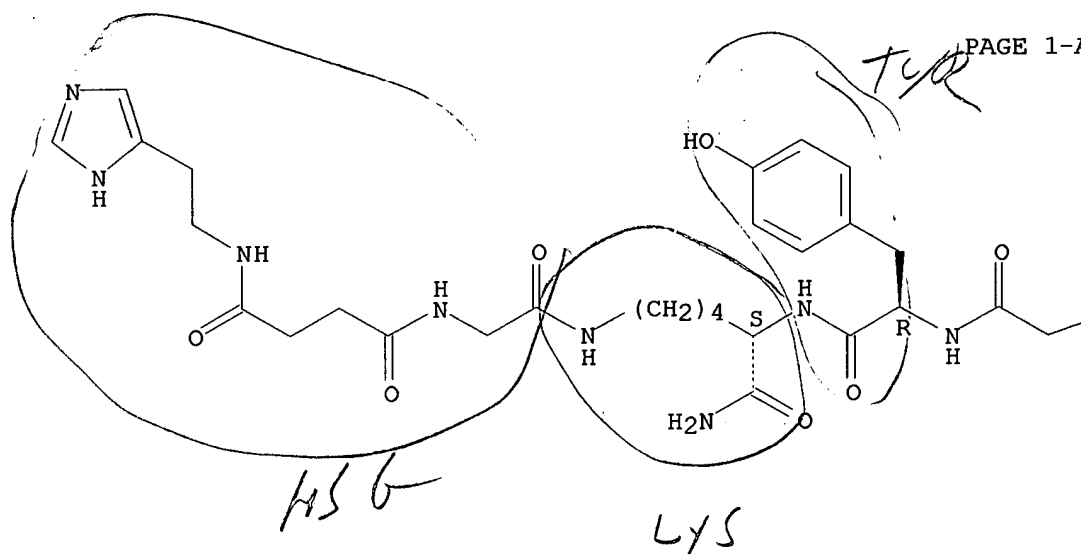


RN 192370-41-5 HCAPLUS

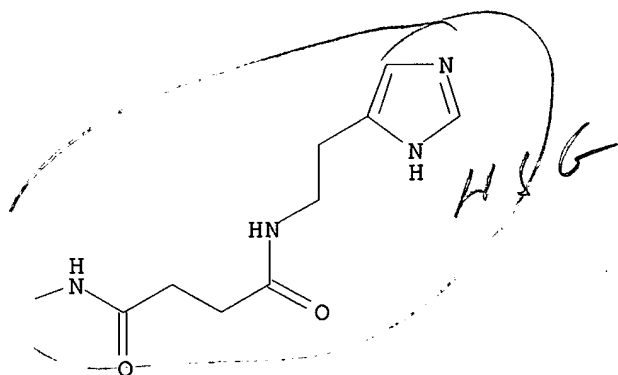
CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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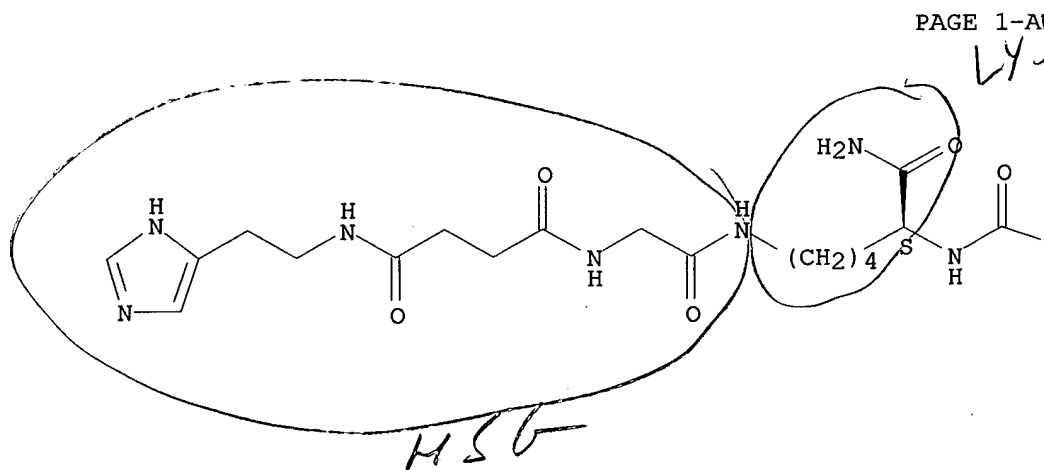


RN 192370-42-6 HCAPLUS

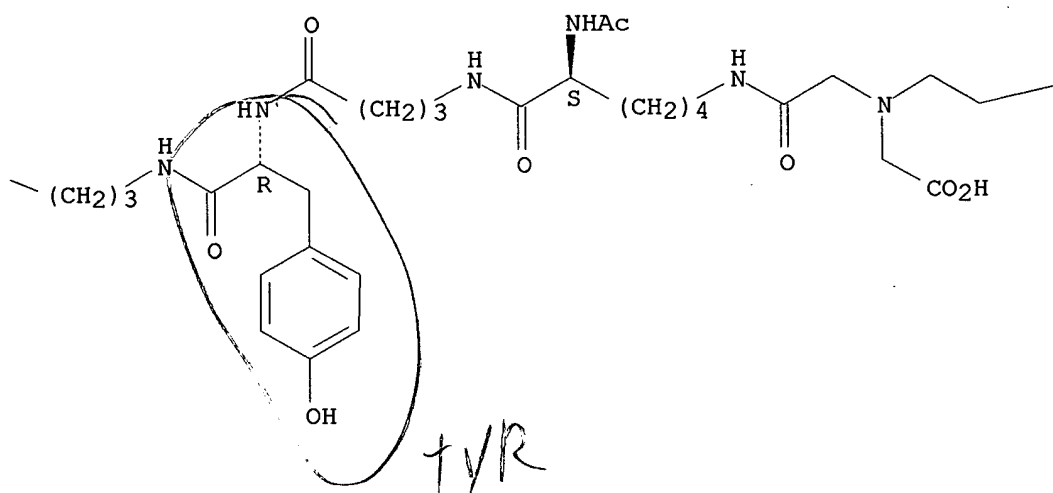
CN L-Lysinamide, N2-acetyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl] (carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-4-aminobutanoyl-D-tyrosyl-4-aminobutanoyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

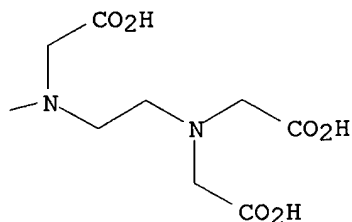
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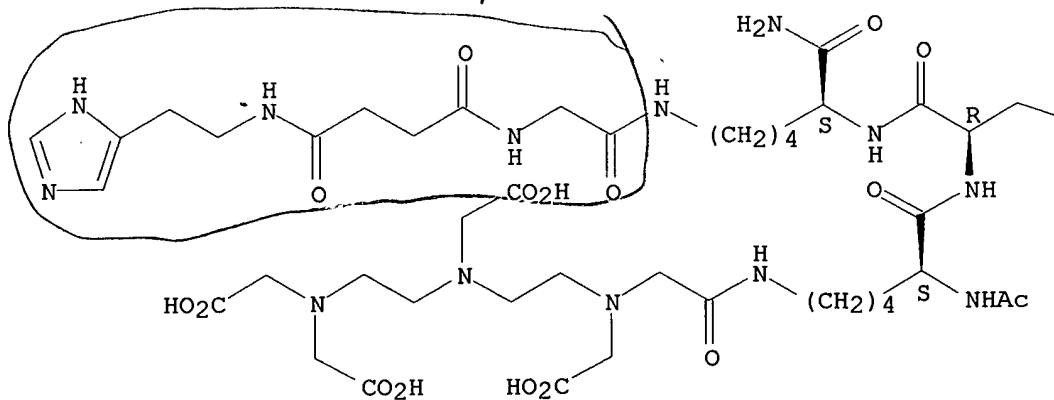


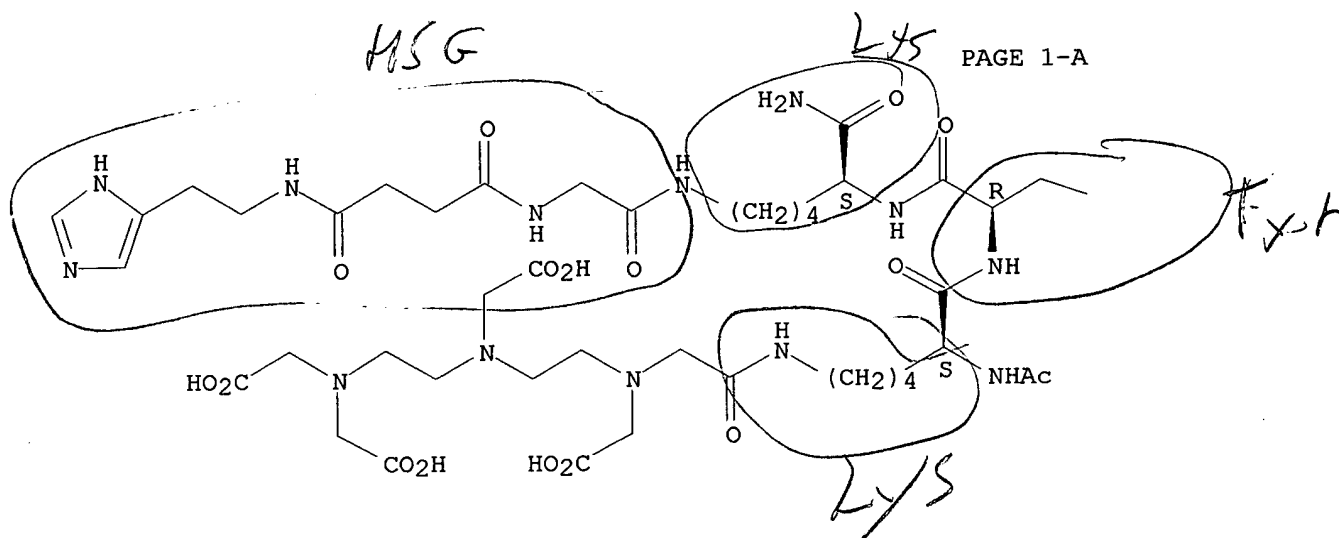
RN 192370-43-7 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

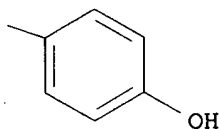
Absolute stereochemistry.

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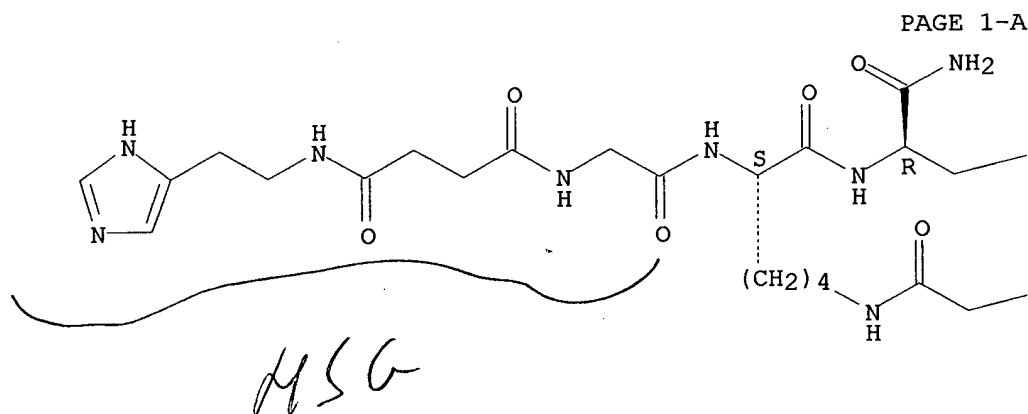
PAGE 1-B



RN 192370-44-8 HCAPLUS

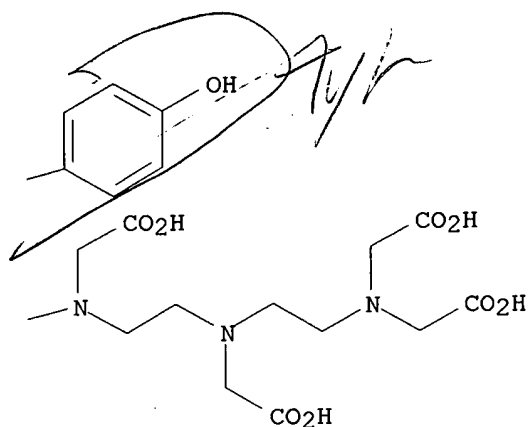
CN D-Tyrosinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.





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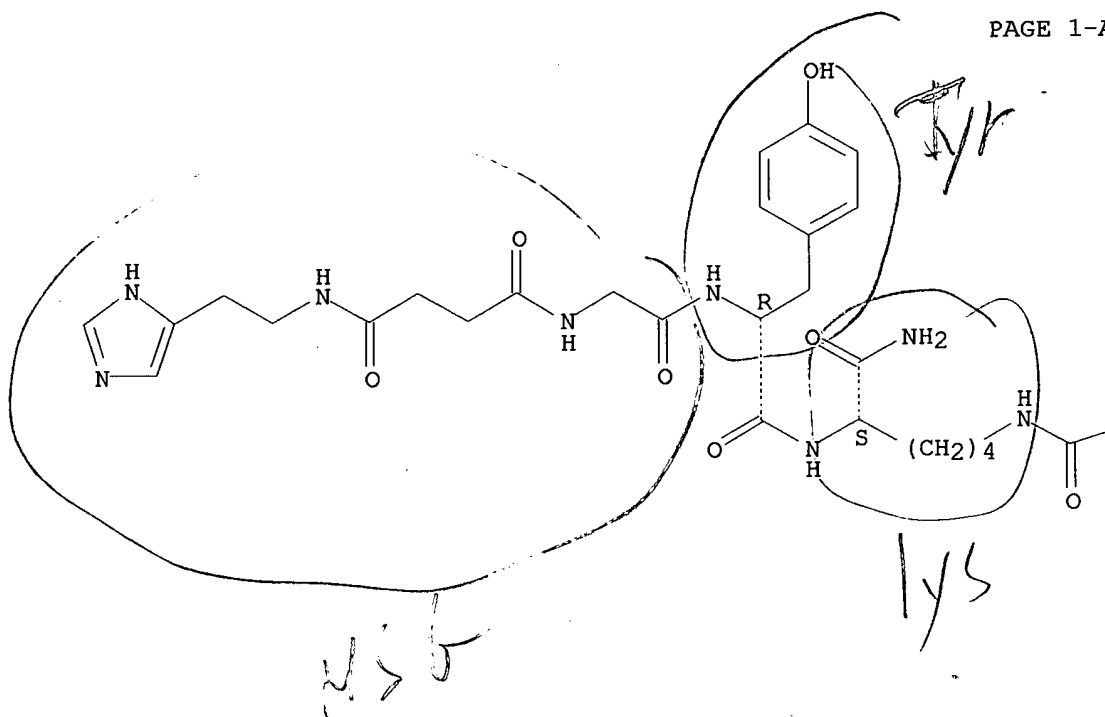


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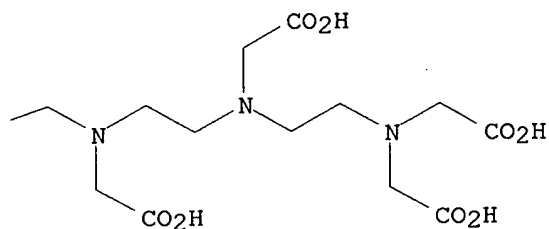
CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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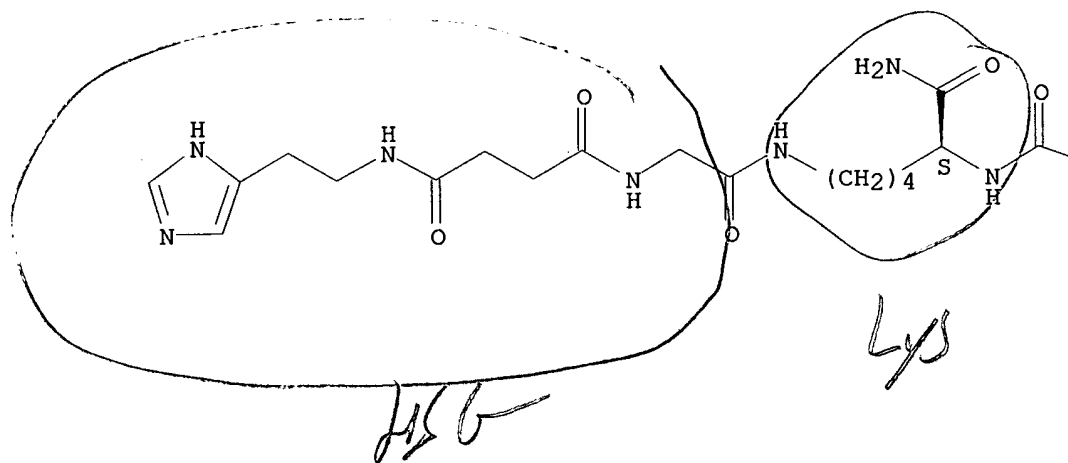


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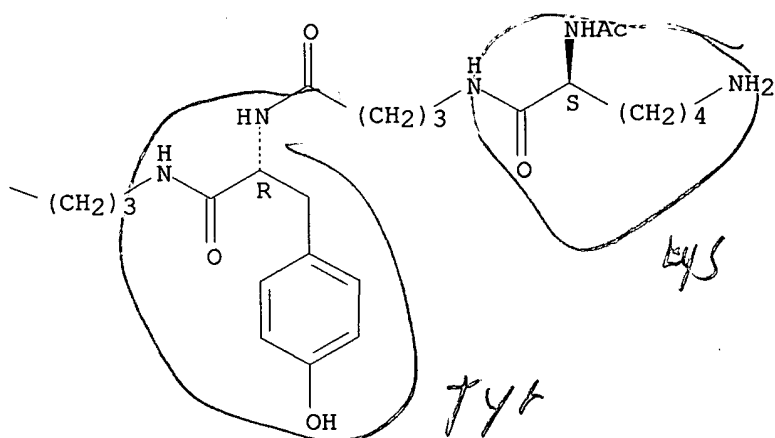
CN L-Lysinamide, N2-acetyl-L-lysyl-4-aminobutanoyl-D-tyrosyl-4-aminobutanoyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI)  
(CA INDEX NAME)

Absolute stereochemistry.

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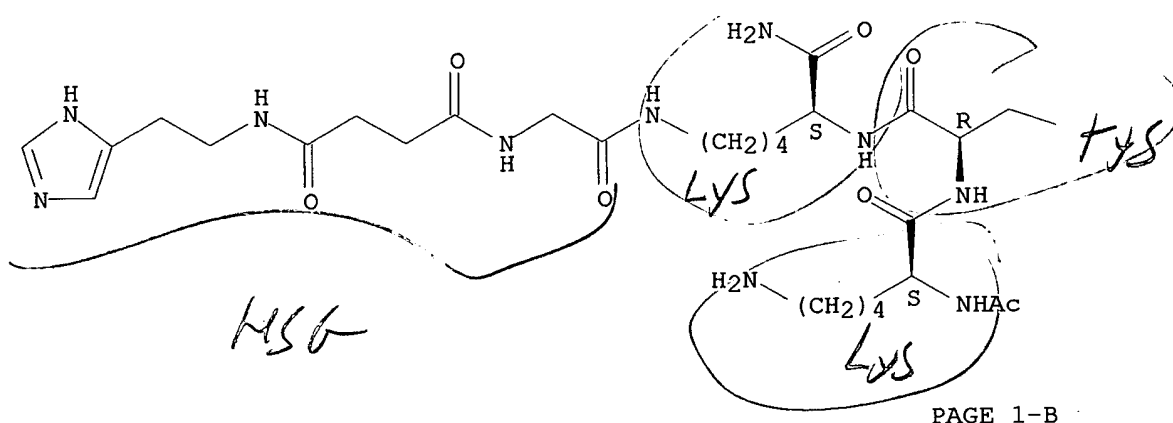


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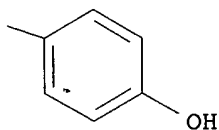
CN L-Lysinamide, N2-acetyl-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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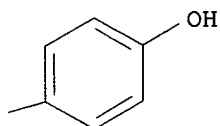
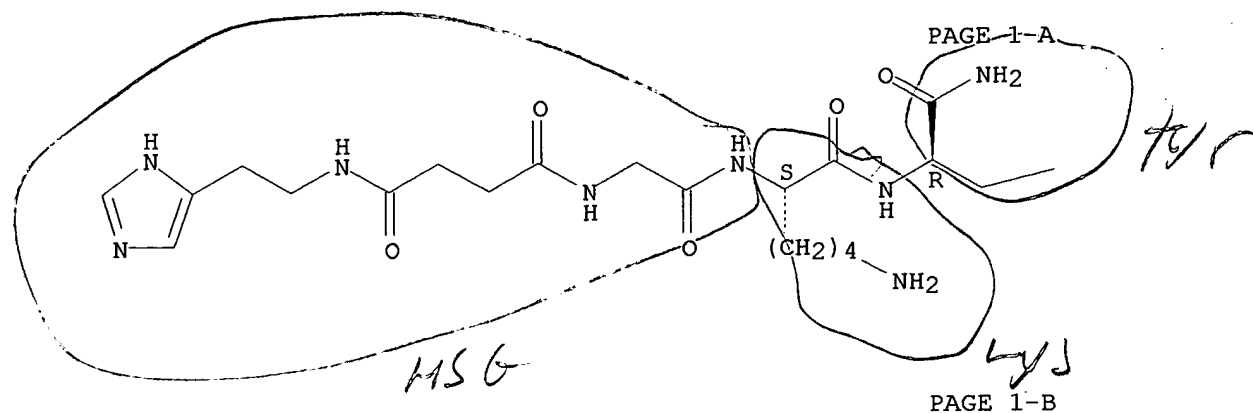
PAGE 1-B



RN 192370-48-2 HCAPLUS

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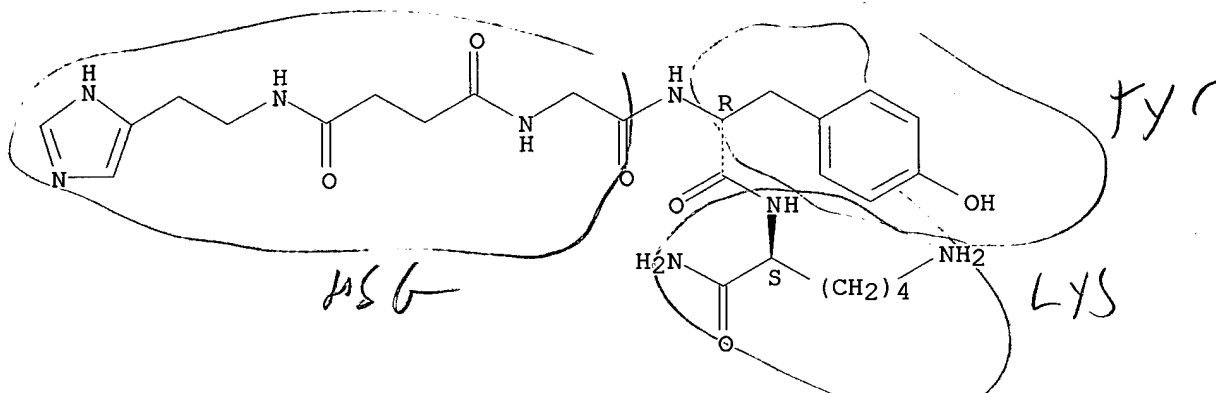
Absolute stereochemistry.



RN 192370-49-3 HCAPLUS

CN L-Lysinamide, N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl-D-tyrosyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L21 ANSWER 6 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1995:979758 HCAPLUS

DOCUMENT NUMBER: 124:111216

TITLE: Intracellular uptake and catabolism of anti-IgM antibodies and bi-specific antibody-targeted hapten by B-lymphoma cells

AUTHOR(S): Manetti, Corine; Doussal, Jean Marc Le; Rouvier, Eric; Gruaz-Guyon, Anne; Barbet, Jacques

CORPORATE SOURCE: Imaging and Therapeutics Department, IMMUNOTECH, Marseille, 13276/9, Fr.

SOURCE: International Journal of Cancer (1995), 63(2), 250-6  
CODEN: IJCNAW; ISSN: 0020-7136

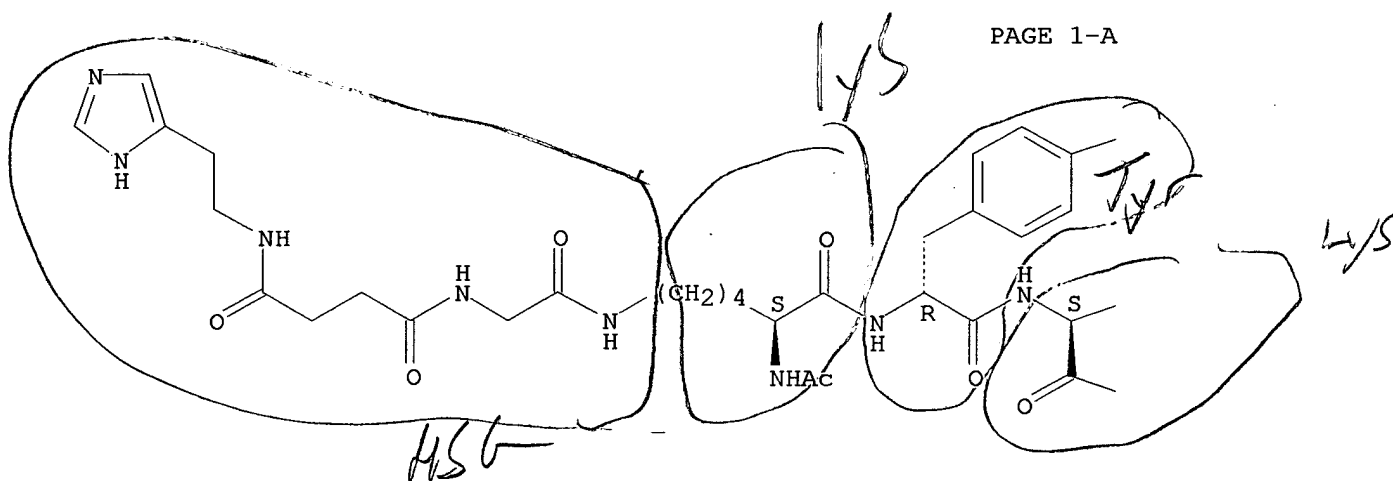
PUBLISHER: Wiley-Liss

DOCUMENT TYPE: Journal

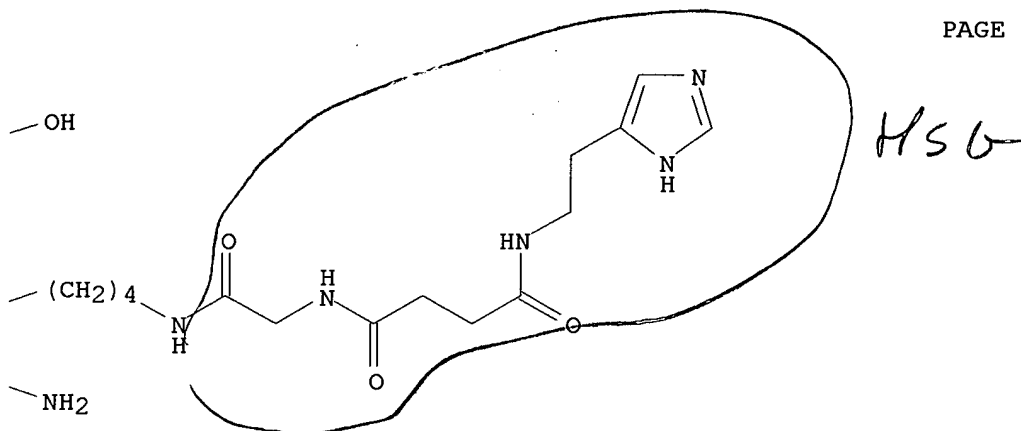
LANGUAGE: English

- AB The efficiency of radioimmunotherapy with iodine-labeled antibodies is often limited by intracellular internalization and catabolism after initial binding to the cellular targets. The authors have developed a technique called affinity enhancement system (AES) which uses bi-specific antibodies to target radiolabeled bivalent haptens to cells. This targeting method has been applied successfully to tumor imaging in colorectal cancer patients and is now considered for therapy. The authors have investigated the potential of this technique to target iodine radioisotopes by comparing it to targeting with covalently iodine-labeled antibodies in a rapidly internalizing antigenic system, the surface IgM of a B-lymphoma cell line. A 5-fold increase in the intracellular retention time of activity as compared to  $^{125}\text{I}$ -labeled  $\text{F(ab')}_2$  or IgG was obsd. The radiolabeled hapten did not undergo any catabolism after internalization. Resistance to cellular proteases and failure of recognition of the hapten by amino acid transporter systems may be potential explanations for these observations. This should make noncovalent targeting, particularly the AES, a method of choice to target modulating antigens for the therapy of malignant hemopathies.
- IT **173039-12-8D**, radiolabeled with indium-111 or iodine-125  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (intracellular uptake and catabolism of anti-IgM antibodies and bi-specific antibody-targeted hapten by B-lymphoma cells)
- RN 173039-12-8 HCAPLUS
- CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



PAGE 1-B



L21 ANSWER 7 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1994:701327 HCAPLUS

DOCUMENT NUMBER: 121:301327

TITLE: preparation of bihaptenic derivatives for binding for technetium or rhenium for diagnosis and therapy and immunological reactants comprising them

INVENTOR(S): Gruaz-Guyon, Anne; Le Doussal, Jean Marc; Delaage, Michel; Barbet, Jacques

PATENT ASSIGNEE(S): Immunotech Partners: Societe Anonyme Dite, Fr.

SOURCE: Eur. Pat. Appl., 13 pp.

CODEN: EPXXDW

DOCUMENT TYPE: Patent

LANGUAGE: French

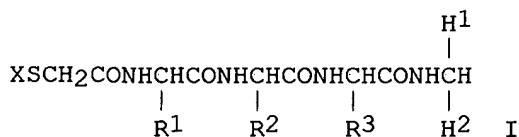
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 595743	A1	19940504	EP 1993-430015	19931026
EP 595743	B1	20010314		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
FR 2697255	A1	19940429	FR 1992-13267	19921027
FR 2697255	B1	19950113		
CA 2109256	AA	19940428	CA 1993-2109256	19931026
AU 9350292	A1	19940512	AU 1993-50292	19931026
AU 669219	B2	19960530		
AT 199728	E	20010315	AT 1993-430015	19931026
ES 2155830	T3	20010601	ES 1993-430015	19931026
JP 06321809	A2	19941122	JP 1993-268835	19931027
PRIORITY APPLN. INFO.:			FR 1992-13267	A 19921027

OTHER SOURCE(S): MARPAT 121:301327

GI



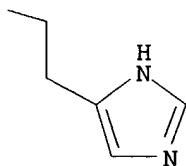
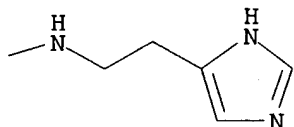
IT 159173-61-2P

RN 159173-61-2 HCAPLUS

Absolute stereochemistry.

The chemical structure shows a bis-lysine derivative. A central chiral center, labeled 'R', is bonded to a p-hydroxybenzyl group (a benzene ring with a para-hydroxyl group and a methylene group) and a lysine side chain. The lysine side chain consists of a methylene group, an amide group, and a lysine residue (a four-carbon chain with an amine group). The structure is symmetrical, with two identical lysine residues attached to the central chiral center. The amide groups are shown with their respective hydrogen atoms, and the lysine residues are shown with their respective amine groups. The central chiral center is also bonded to a hydrogen atom and a lysine side chain. The lysine side chain consists of a methylene group, an amide group, and a lysine residue (a four-carbon chain with an amine group). The structure is symmetrical, with two identical lysine residues attached to the central chiral center. The amide groups are shown with their respective hydrogen atoms, and the lysine residues are shown with their respective amine groups.

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IT 159173-58-7P 159173-59-8P

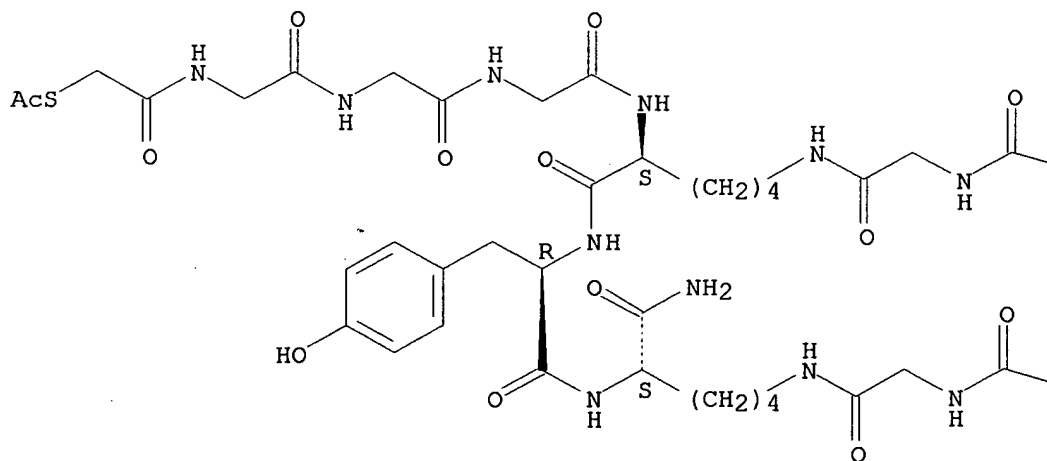
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, for diagnosis and therapy kits)

RN 159173-58-7 HCAPLUS

CN L-Lysinamide, N-[(acetylthio)acetyl]glycylglycylglycyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

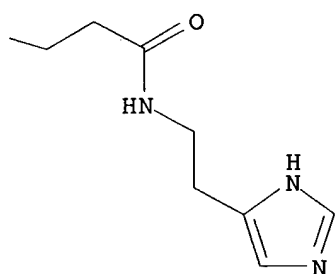
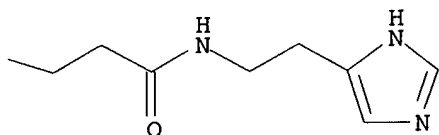
Absolute stereochemistry.

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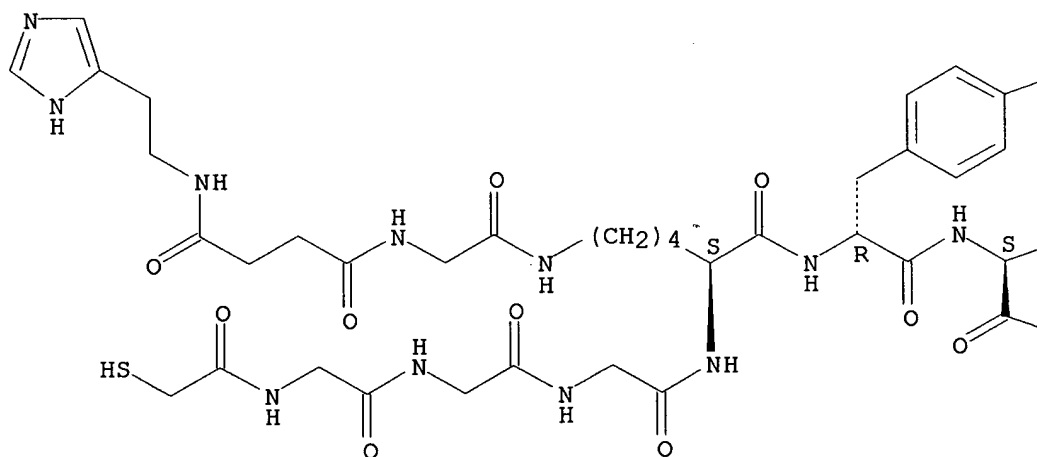


RN 159173-59-8 HCAPLUS

CN L-Lysinamide, N-(mercaptoacetyl)glycylglycylglycyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-D-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



NC(=O)CCCCNC(=O)NCCCCNC(=O)NCCCCc1c[nH]c2ccccc12

L21 ANSWER 8 OF 9 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1992:17814 HCAPLUS

DOCUMENT NUMBER: 116:17814

TITLE: Radiolabeled hapten-derivatized peptides for tumor imaging with bispecific antibody conjugates

AUTHOR(S): Gruaz-Guyon, A.; Gras-Masse, H.; Le Doussal, J. M.

CORPORATE SOURCE: CHU St. Antoine, Paris, 75012, Fr.

SOURCE: Pept. 1990, Proc. Eur. Pept. Symp., 21st (1991), Meeting Date 1990, 822-5. Editor(s): Giralt, Ernest; Andreu, David. ESCOM Sci. Publ.: Leiden, Neth. CODEN: 57HNAI

DOCUMENT TYPE: Conference

LANGUAGE: English

AB Tumor imaging with <sup>111</sup>In- or <sup>125</sup>I-labeled monoclonal antibody F(ab')<sub>2</sub> fragments derivatized with bivalent haptens of histamine and DTPA was examd. in nude mice grafted with A375 human melanoma cells. Tumor targeting with F(ab)'-F(ab)' conjugates was better than that with F(ab')<sub>2</sub>-F(ab)' and tumor labeling with DTPA haptens was better than with dihistamine labeling.

IT **136687-41-7D**, radiolabeled monoclonal antibody F(ab')<sub>2</sub> fragment conjugates **138168-53-3D**, radiolabeled monoclonal antibody F(ab')<sub>2</sub> fragment conjugates

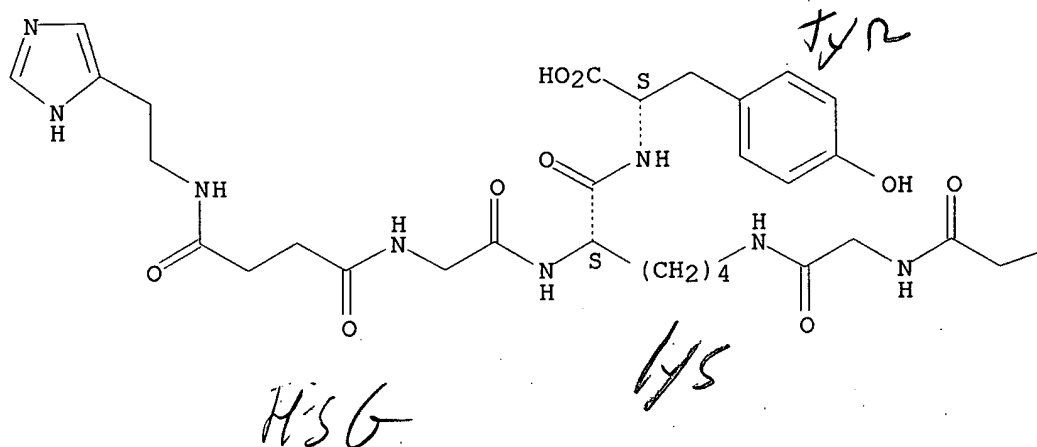
RL: BIOL (Biological study)  
(imaging with, of tumor)

RN 136687-41-7 HCAPLUS

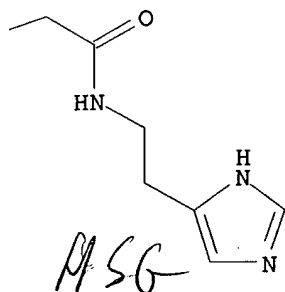
CN L-Tyrosine, N-[N<sub>2</sub>,N<sub>6</sub>-bis[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



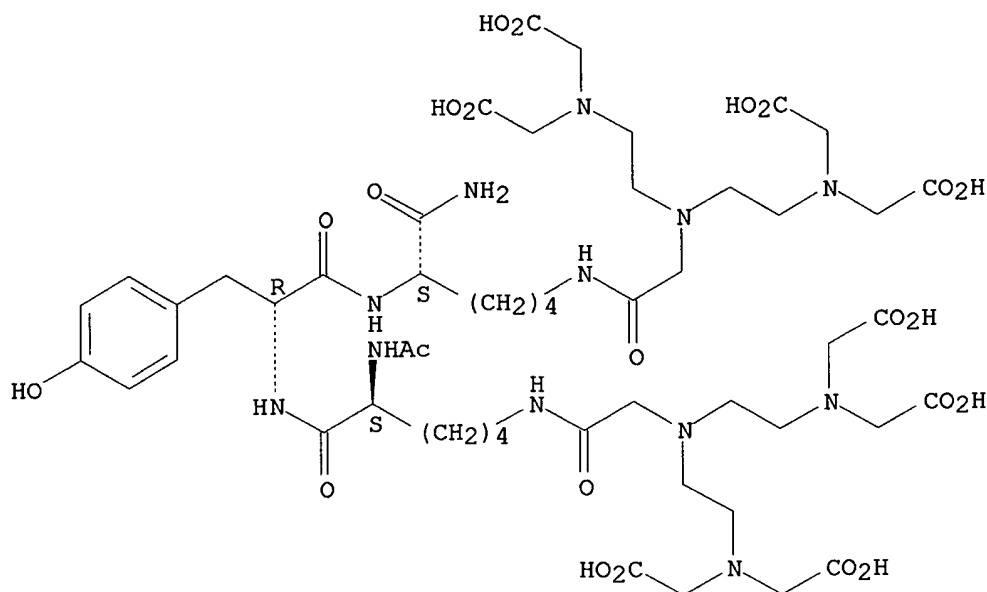
PAGE 1-B



RN 138168-53-3 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycyl]-  
 1]-L-lysyl-D-tyrosyl-N6-[N,N-bis[2-[bis(carboxymethyl)amino]ethyl]glycyl]-  
 (9CI) (CA INDEX NAME)

Absolute stereochemistry.



*This is same as  
ited  
US 823,746*

L21 ANSWER 9 OF 9 HCAPLUS COPYRIGHT 2003 ACS  
 ACCESSION NUMBER: 1991:578300 HCAPLUS  
 DOCUMENT NUMBER: 115:178300  
 TITLE: Hydrophilic derivatives containing effector group and  
 2 haptens, their immunodiagnostic and  
 immunotherapeutic use, and kits and immunological  
 reagents containing them  
 INVENTOR(S): Barbet, Jacques; Delaage, Michel; Gruaz-Guyon, Anne;  
 Le Doussal, Jean Marc  
 PATENT ASSIGNEE(S): Immunotech Partners, Fr.  
 SOURCE: Eur. Pat. Appl., 8 pp.  
 CODEN: EPXXDW  
 DOCUMENT TYPE: Patent  
 LANGUAGE: French  
 FAMILY ACC. NUM. COUNT: 1  
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 419387	A1	19910327	EP 1990-430018	19900920
EP 419387	B1	19961120		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FR 2652004	A1	19910322	FR 1989-12622	19890921
FR 2652004	B1	19941028		
CA 2025607	AA	19910322	CA 1990-2025607	19900918
CA 2025607	C	20010807		
US 5274076	A	19931228	US 1990-584003	19900918
AU 9063034	A1	19910328	AU 1990-63034	19900920
AU 638488	B2	19930701		
JP 03173900	A2	19910729	JP 1990-248965	19900920
JP 2914737	B2	19990705		
AT 145338	E	19961215	AT 1990-430018	19900920
ES 2094750	T3	19970201	ES 1990-430018	19900920

## PRIORITY APPLN. INFO.:

FR 1989-12622 A 19890921

AB Compds. are prepd. which contain 2 hydrophilic haptens and an effector group (an isotope or group that can be labeled with isotope, or an active principle or group to which an active principle can be attached), bonded by a nonpolymer connecting chain. The effector group is e.g. a scintigraphic radioisotope or a cytotoxic agent. The compds. are used in conjunction with (monoclonal) antibodies to specific cell types conjugated with (monoclonal) antibodies recognizing the hapten of the compd. and are useful for immunodiagnosis and immunotherapy. Thus, N.alpha.-DTPA-tyrosyl-N.epsilon.-DTPA-lysine, prepd. from tyrosyllysine and DTPA cyclic anhydride, was labeled with  $^{111}\text{In}$ , and the resulting  $^{111}\text{In}$  complex (I) was used in the immunoscintigraphic visualization of melanoma in nude mice. The mice, contg. human melanoma A375, were injected with a bispecific conjugate of a monoclonal anti-human melanoma F(ab')<sub>2</sub> fragment linked to a monoclonal anti-DTPA-Ir F(ab')<sub>2</sub> fragment. Later, I was injected and gamma camera images were obtained over time. The fixation obsd. was specific; the tumor did not accumulate significant amts. of radioactivity when the bispecific antibody conjugate was not injected or when the conjugate used had specificity for an antigen assocd. with another tumor. When  $^{111}\text{In}$ -DTPA replaced I, the radioactivity was excreted rapidly and little specific fixation was obsd.

IT 136687-41-7P 136687-42-8P 136687-43-9P

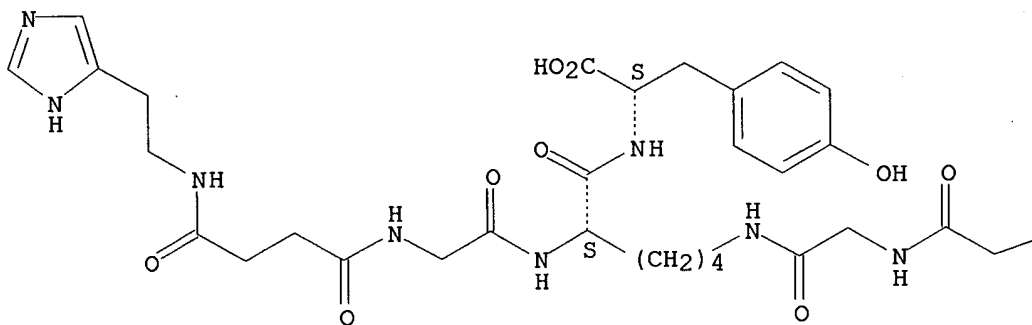
RL: SPN (Synthetic preparation); PREP (Preparation)  
(prepn. of, for immunodiagnosis and immunotherapy)

RN 136687-41-7 HCAPLUS

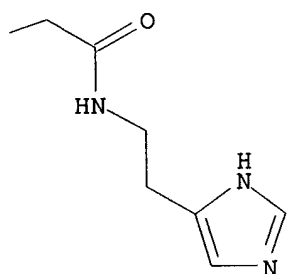
CN L-Tyrosine, N-[N<sub>2</sub>,N<sub>6</sub>-bis[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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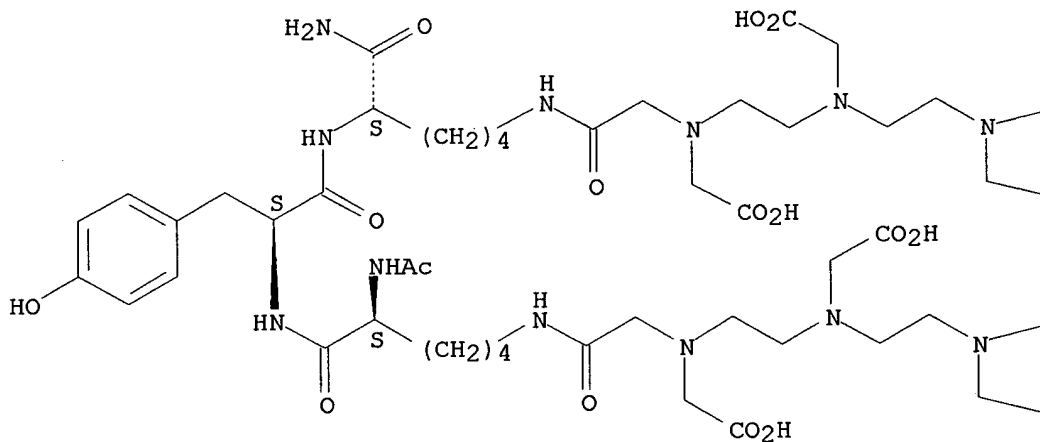


RN 136687-42-8 HCAPLUS

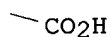
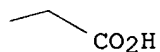
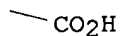
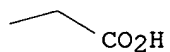
CN L-Lysinamide, N2-acetyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]-L-lysyl-L-tyrosyl-N6-[N-[2-[[2-[bis(carboxymethyl)amino]ethyl](carboxymethyl)amino]ethyl]-N-(carboxymethyl)glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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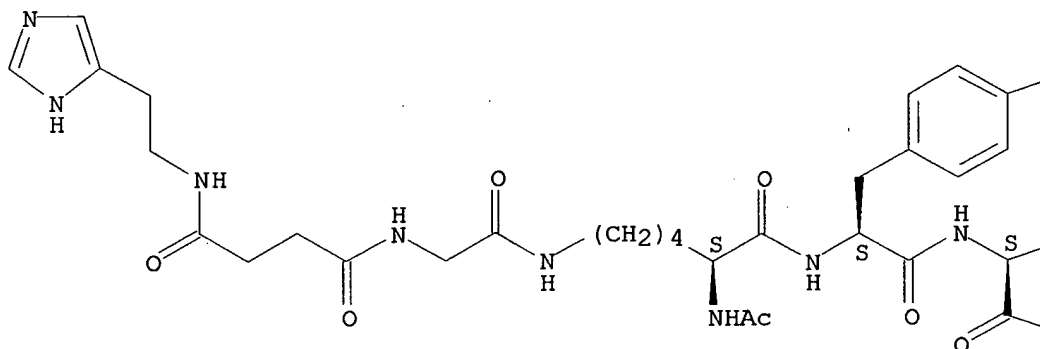


RN 136687-43-9 HCAPLUS

CN L-Lysinamide, N2-acetyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]-L-lysyl-L-tyrosyl-N6-[N-[4-[[2-(1H-imidazol-4-yl)ethyl]amino]-1,4-dioxobutyl]glycyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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